

1980

or prognose, inflammatory conditions, both chronic and acute conditions, including, but not limited to, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, and resulting from over
5 production of cytokines (e.g., TNF or IL-1.).

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or
10 differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents,
15 etc), without necessarily eliciting an immune response.

Additional preferred embodiments of the invention include, but are not limited to, the use of polypeptides, antibodies, polynucleotides and/or agonists or antagonists in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-
20 pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

Administration to an animal (including, but not limited to, those listed above, and also
25 including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741.

30 A vaccine adjuvant that enhances immune responsiveness to specific antigen.

An adjuvant to enhance tumor-specific immune responses.

An adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

An adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and Plasmodium (malaria).

An adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

As a stimulator of B cell responsiveness to pathogens.

As an activator of T cells.

As an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

As an agent to induce higher affinity antibodies.

5 As an agent to increase serum immunoglobulin concentrations.

As an agent to accelerate recovery of immunocompromised individuals.

As an agent to boost immunoresponsiveness among aged populations.

As an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect
10 to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but
15 prior to full recovery of B cell populations.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS,
20 bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

As an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections
25 (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

As a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists
30 of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonization of

antigen presentation may be useful as an anti- tumor treatment or to modulate the immune system.

As an agent to direct an individuals immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

5 As a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

10 As a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

As a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

As a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

15 As an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

As a means of activating T cells.

As a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leshmania.

20 As pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recover.

As a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

25 Additionally, polypeptides or polynucleotides of the invention, and/or agonists thereof, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

All of the above described applications as they may apply to veterinary medicine.

30 Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, or ribozymes. These would be expected to reverse many of the activities of the ligand described above as well as find clinical or practical application as:

A means of blocking various aspects of immune responses to foreign agents or self. Examples include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and pathogens.

5 A therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythramatosus and MS.

An inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

10 An inhibitor of graft versus host disease or transplant rejection.

A therapy for B cell and/or T cell malignancies such as ALL, Hodgkins disease, non-Hodgkins lymphoma, Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases.

15 A therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonalgammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonalgammopathies, and plasmacytomas.

A therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

A means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

20 An immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

25 In another embodiment, administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention, may be used to treat or prevent IgE-mediated allergic reactions including, but not limited to, asthma, rhinitis, and eczema.

The agonists and antagonists may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

30 The agonists or antagonists may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain auto-immune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and

insulin-dependent diabetes. The antagonists or agonists may also be employed to treat infectious diseases including silicosis, sarcoidosis, idiopathic pulmonary fibrosis by, for example, preventing the recruitment and activation of mononuclear phagocytes. They may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration. The antagonists or agonists or may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

Antibodies against polypeptides of the invention may be employed to treat ARDS.

Agonists and/or antagonists of the invention also have uses in stimulating wound and tissue repair, stimulating angiogenesis, stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to treat or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent (1) cancers or neoplasms and (2) autoimmune cell or tissue-related cancers or neoplasms. In a preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or

1986

antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent acute myelogeneous leukemia. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, chronic myelogeneous leukemia, multiple myeloma, non-Hodgkins lymphoma, and/or Hodgkins disease.

In another specific embodiment, polynucleotides or polypeptides, and/or agonists or antagonists of the invention may be used to treat, diagnose, prognose, and/or prevent selective IgA deficiency, myeloperoxidase deficiency, C2 deficiency, ataxia-telangiectasia, DiGeorge anomaly, common variable immunodeficiency (CVI), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome.

Examples of autoimmune disorders that can be treated or detected are described above and also include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of

1987

polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prognosed, prevented, and/or diagnosed using antibodies against the polypeptide of the invention.

As an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Additionally, polynucleotides, polypeptides, and/or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis

and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome,

1989

Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be detected and/or treated by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to neoplasms located in the: liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Hyperproliferative Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response.

1990

Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present

invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

1993

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

5 The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing
10 antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a
15 dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other
20 polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the
25 present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis.
30 Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-

1994

mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the
5 activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue
10 React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of
15 proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions
20 containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic,
25 hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly,
30 such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

1995

Cardiovascular Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

5 Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, 10 levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogly of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid 15 heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, 20 myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, 25 extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, 30 ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

1996

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis,

1997

carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar
5 insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

10 Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and
15 Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical
20 administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are
25 described in more detail herein.

Anti-Angiogenesis Activity

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell*
30 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and

1998

spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered

1999

topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical
5 administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating
10 other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis,
15 retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque
20 neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar
25 or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of
30 hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also

2000

provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated
5 with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g.,
10 reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically
15 effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may
20 become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact
25 lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily.
30 Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within

further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic

2002

retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

5 Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

10 Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

15 Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for
20 example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations,
25 ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers
30 (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

 In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have

2003

occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

5 Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an
10 area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated
15 with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

20 Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the
25 tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

30 Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one

2004

embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention
5 may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

10 Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes
15 such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

20 Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate,
25 molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes
30 include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine

2005

sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including
5 for example, proline analogs, cishydroxyproline, d,L-3,4-dehydropoline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin;
10 Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316,
15 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of apoptosis that
20 could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,
25 lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as
30 herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides,

2006

polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host

2007

disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

5

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avascular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentum graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as

2008

agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid

2009

more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or

2010

antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

5 The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either
10 a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous
15 system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system
20 associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system
25 is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic
30 acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes

2011

(diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful

2012

according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
5 (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be
10 detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be
15 measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor
20 neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory
25 Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles,
30 including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral

2013

disorders include, but are not limited to, Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

5 In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or
10 injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral
15 hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a
20 process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can
25 be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase
30 complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms,

2014

canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

2015

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which
5 includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna,
10 and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria
15 Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uve-meningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis
20 syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous
25 system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerolosis which includes adrenoleukodystrophy, encephalitis
30 periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis,

2016

transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as
5 epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolidosis such as fucosidosis, neuronal ceroid-
10 lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele,
15 meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary
20 Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include
25 agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation,
30 hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle

2017

spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, 5 quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and 10 vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex 15 Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes 20 Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic 25 Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, 30 polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as

2018

causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic
5 Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

10 **Infectious Disease**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either
15 enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms
20 that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae
25 (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus).
30 Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E,

2019

Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g.,
5 Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the
10 invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the
15 present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis,
20 Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria
25 meningitidis, Pasteurellaceae Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia,
30 endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme

2020

Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g.,
5 cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

10 Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and
15 Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis.
20 polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a
25 polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

30 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to

2021

repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

5 Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

10 Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could
15 be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

 Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and
20 differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system
25 diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

30 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or

2022

endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially

2023

containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor

molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not

2025

necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and 3[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of 3[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of 3[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide

of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Colon Cancer Antigen Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind the colon cancer antigens of the invention, and the colon cancer antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the colon cancer antigens of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:

- a. contacting a colon cancer antigen of the invention with a plurality of molecules; and
- b. identifying a molecule that binds the colon cancer antigen.

The step of contacting the colon cancer antigen of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the colon cancer antigen on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized colon cancer antigen. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized colon cancer antigen of the invention. The molecules having a selective affinity for the colon cancer antigen can then be purified by affinity selection. The nature of the solid support, process for attachment of the colon cancer antigen of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be

expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by a colon cancer antigen, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the colon cancer antigen and the individual clone. Prior to contacting the colon cancer antigen of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for a colon cancer antigen of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound colon cancer antigen, or alternatively, unbound polypeptides, from a mixture of the colon cancer antigen of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the protein of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature* 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al., 1993,

Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include, but are not limited to, those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one

monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a colon cancer antigen can be carried out by contacting the library members with a colon cancer antigen of the invention immobilized on a solid phase and harvesting those library members that bind to the colon cancer antigen. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, *Nature* 340:245-246; Chien et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:9578-9582) can be used to identify molecules that specifically bind to a colon and/or colon cancer related protein of the invention.

Where a colon cancer antigen of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can

be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

5 As mentioned above, in the case of a colon and/or colon cancer related protein of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a colon and/or colon cancer related protein of the invention binding polypeptide has in the range of 15-100
10 amino acids, or 20-50 amino acids.

The selected colon cancer antigen protein of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

15

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a colon cancer antigen of the invention.

20 As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method
25 for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

30 In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

2031

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of

Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., *Neurochem.* 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the

art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of shown in Table 1 could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5', 3'- or coding region

of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

5 The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 10 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-15 976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

 The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 20 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 25 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-30 3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of

SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat the diseases described herein. Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Other Activities

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in

treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

5 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

10 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte
15 growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may
20 also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

25 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may
30 also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Id in Table 1 which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit
5 Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300,
10 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and
15 contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least
20 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at
25 least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y wherein Y is any
30 integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete

amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

5 Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

10 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown
15 above for said cDNA library identifier.

 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited
20 with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in
25 Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

 Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid
30 sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an

amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the
5 ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10
10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least
15 two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA
20 library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence
25 which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a
30 cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide
5 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers
10 shown above for said cDNA library identifier.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the
15 recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a
20 human protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Protein of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Protein of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a protein encoded by a human cDNA clone identified by a
25 cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a
30 Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

2048

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding
5 fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., including, but not limited to, colon or colon cancer cells or tissues), which method comprises administering to such an individual a
10 Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not
15 intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 9 identifies the vectors used to construct the cDNA library from which each clone was isolated.

Table 9.

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HASA	Uni-ZAP XR	LP03
HFCA HFCD HFCE HFCF	Uni-ZAP XR	LP13
HFKF	Uni-ZAP XR	LP13
HE8A HE8B HE8C HE8D HE8E HE8F HE8N HE8O HE8P HE8Q HE8T HE8U	Uni-ZAP XR	LP03
HGBA HGBG HGBH	Uni-ZAP XR	LP13
HGBB	Uni-ZAP XR	LP03
HHFA	pBluescript	NA
HLHA HLHB HLHC HLHD HLHE HLHG	Uni-ZAP XR	LP03
HOOA	pBluescript	NA
HPLB	Uni-ZAP XR	NA
HPMD HPME HPMF	Uni-ZAP XR	LP03
HPRA	Uni-ZAP XR	LP13
HSIA HSIC HSID HSIE	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEJ HTEK	Uni-ZAP XR	LP13
HTPA HTPC	Uni-ZAP XR	LP03
HTTB HTTC HTTD HTTE HTTF	Uni-ZAP XR	LP13
HAPA HAPC	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETG HETH HETI HETJ	Uni-ZAP XR	LP03
HHFB HHFC HHFG HHFH HHFI	Uni-ZAP XR	LP13
HHPE HHPG	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCEC HCED HCEE HCEF HCEI HCEM HCEN HCEO HCEP	Uni-ZAP XR	LP03
HUVC HUVD	Uni-ZAP XR	LP13
HUKB HUKF	Lamda ZAP II	LP13
HTHC HTHD	Uni-ZAP XR	LP13
HSTA	Uni-ZAP XR	LP13
HTAE	Uni-ZAP XR	LP13
HLEA	Uni-ZAP XR	PA005 Phage
HFEA HFEB	Uni-ZAP XR	LP13
HJPA HJPC	Uni-ZAP XR	LP13
HCNA	Lambda ZAP II	LP01
HTSG	pBS	LP05
HLTA HLTB HLTC HLTD HLTE	Uni-ZAP XR	LP03
HAHS	pBluescript	LP13
HALS	Uni-ZAP XR	LP13
HE6B HE6F HE6G	Uni-ZAP XR	LP04
HF6S	pBluescript	LP13
HPMS	pBluescript	LP03
HTYS	pBluescript	NA
HRDB HRDD HRDE HRDF	Uni-ZAP XR	LP03
HCAB	Uni-ZAP XR	LP13
HL3A	Uni-ZAP XR	PA005 Phage
HRGD	Uni-ZAP XR	LP13
HSSE HSSG HSSI	Uni-ZAP XR	LP04
HSUA HSUB	Uni-ZAP XR	LP03
HT3A	Uni-ZAP XR	NA

2050

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HT4C	Uni-ZAP XR	LP03
HE9F HE9H HE9M HE9N HE9O HE9P HE9Q HE9R HE9S HE9T	Uni-ZAP XR	LP13
HEPA HEPB	Uni-ZAP XR	LP04
HSFA	Uni-ZAP XR	LP13
HATA HATB HATC HATE	Uni-ZAP XR	LP13
HT3B	Uni-ZAP XR	PA005 Phage
HSNA	Uni-ZAP XR	LP04
HPFC	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2O	Uni-ZAP XR	LP13
HE2B HE2C HE2F HE2P	Uni-ZAP XR	LP13
HCBB	Uni-ZAP XR	NA
HFGA	Uni-ZAP XR	LP03
HNEA HNED	Uni-ZAP XR	LP13
HBGB	Uni-ZAP XR	LP03
HKCA	Uni-ZAP XR	PA005 Phage
HKLA	Lambda ZAP II	PA005 Phage
HBNA	Uni-ZAP XR	LP03
HCET	pBluescript	PA005 Phage
HKCS HKCU	pBluescript	LP03
HKCT	pBluescript	PA005 Phage
HLIS	pBluescript	LP13
HLHS HLHT	pBluescript	LP13
HPRT	pBluescript	PA005 Phage
HPTT	Uni-ZAP XR	LP13
HRGS	pBluescript	LP03
HSUS	pBluescript	LP13
HT2S	Uni-ZAP XR	NA
HCNS	pBluescript	PA005 Phage
HCNU	pBluescript	PA005 Phage
HKLR	pBluescript	PA005 Phage
HKLS	pBluescript	PA005 Phage
HKTA	Uni-ZAP XR	PA005 Phage
HHFU	pBluescript	NA
HE8S	Uni-ZAP XR	LP03
HCDC HCDE	Uni-ZAP XR	LP03
HOAA	Uni-ZAP XR	LP13
HTLA HTLD HTLE	Uni-ZAP XR	LP03
HLMD	Uni-ZAP XR	PA005 Phage
HLMI HLMM	Lambda Zap II	LP01

2051

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
H6EA H6EB	Uni-ZAP XR	LP03
HCEV HCEY	Uni-ZAP XR	LP03
HCQA HCQB	Lambda Zap II	LP01
HTOA HTOD HTOH HTOJ	Uni-ZAP XR	LP13
HTXC HTXF	Uni-ZAP XR	LP03
HMEC HMEE HMEG HMEI HMEK	Lambda Zap II	LP01
HMEB	Lambda Zap II	LP13
HNFE HNFF HNFG HNFH	Uni-ZAP XR	LP03
HKEA	ZAP express	PA005 Phage
HMGB	Uni-ZAP XR	LP13
HMHB	Uni-ZAP XR	PA005 Phage
HAUA HAUB	Uni-ZAP XR	LP13
HAQB	Uni-ZAP XR	LP13
HCWH	ZAP express	LP02
HCUC	ZAP express	LP02
HSVB HSVC	Uni-ZAP XR	LP03
HPXA	pBluescript	NA
HBJE HBJF HBJJ HBJM	Uni-ZAP XR	LP13
HCRB	Uni-ZAP XR	LP03
HODA HODB HODC HODD	Uni-ZAP XR	LP13
HDSA	Uni-ZAP XR	LP03
HLQA HLQB	Lambda Zap II	LP01
HHGC HHGD	Lambda Zap II	LP01
HCPA	Uni-ZAP XR	LP13
HMWA HMWB HMWD HMWF HMWH HMWI	Uni-ZAP XR	LP03
HERA	Uni-ZAP XR	LP13
HGLA	Uni-ZAP XR	LP13
HWTB HWTC	Uni-ZAP XR	LP13
HLLC	pCMVSPORT1	PA005 DNA
HLIB HLIC	pCMVSPORT1	LP12
HKDB	pCMVSPORT1	NA
HRKA	pBluescript	PA005 Phage
HOSX	pBluescript	PA005 Phage
HEAA	Uni-ZAP XR	LP13
HBCB HBCC	Uni-ZAP XR	LP21
HHBE HHBF HHHB	pCMVSPORT1	LP12
HBBB	pCMVSPORT1	LP12
HLJB HLJD HLJE	pCMVSPORT1	LP12
HSEB	pCMVSPORT1	NA
HNAA	pSPORT1	NA
HBSA	Uni-ZAP XR	LP04
HBBM	pCMVSPORT1	NA
HADM	pBluescript	NA
HMKA HMKC	pSPORT1	LP12
HFVH HFVI HFVJ HFVK	pBluescript	LP03
HKIM	Lambda Zap II	PA005 Phage

2052

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HCUD HCUE HCUG	ZAP express	LP02
HKIS	pBluescript	NA
HSDS	pBluescript	LP13
HBAG HBAH	pSport1	NA
HUSG HUSI HUSJ	pSport1	LP10
HUSX HUSY HUSZ	pSport1	LP10
HOFM	pCMVSPORT 2.0	LP07
HNFI	pBluescript	LP03
HBMC HBMD	pBluescript	LP03
HCFB HCFC HCFD	pSport1	LP12
HCFL HCFM HCFN HCFO	pSport1	LP12
HPTW	pBluescript	PA005 Phage
HADC HADF	pSport1	LP10
HOVA HOVC HOVD HOVE	pSport1	LP10
HKML HKMM	pBluescript	LP03
HUSF	pBluescript	NA
HOGA HOGB HOGC HOGD HOGE	pCMVSPORT 2.0	LP12
HTWB HTWC HTWD HTWE HTWF	pSport1	LP10
HBXF	ZAP express	LP02
HEOA	pBluescript	PA005 DNA
HSDX	pBluescript	LP13
HMMA	pSport1	LP12
HLYA HLYB HLYC HLYD HLYE HLYG	pSport1	LP10
HCGL	pCMVSPORT 2.0	LP07
HSDZ	pBluescript	LP13
HEON HEOQ HEOS	pSport1	LP10
HCGB	pSport1	LP10
HADT	pBluescript	NA
HTDA	pSport1	LP12
HSPA HSPB	pSport1	LP10
HSPM	pSport1	LP10
HCHA HCHB HCHC	pSport1	LP10
HCHM HCHO	pSport1	LP10
HDLA	pCMVSPORT 2.0	LP07
HDTA HDTB HDTD HDTE HDTG HDTH HDTI HDTJ HDTK HDTL HDTM	pCMVSPORT 2.0	LP07
HTJM HTJN	pCMVSPORT 2.0	LP12
HCIA	pSport1	LP10
H6BS	Uni-ZAP XR	LP03
HKAA HKAB HKAC HKAD HKAE HKAF HKAH KAJ HKAK HKAO	pCMVSPORT 2.0	LP07
HDAA HDAB HDAC	pSport1	LP10
HUFA HUFB HUFC HUFD HUFF	pSport1	LP10
HLDB HLDC HLDD	pCMVSPORT 3.0	LP08

2053

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HLDN HLDO	pCMVSPORT 3.0	LP08
HNDA	pCMVSPORT 2.0	LP07
HMTA HMTB	pCMVSPORT 3.0	LP08
HNTA HNTB HNTC HNTD HNTE	pCMVSPORT 3.0	LP08
HNTM	pSPORT1	LP10
HDPA HDPB HDPC HDPF HDPG HDPH HDPI HDPJ HDPK HDPL HDPR HDPS HDPT HDPV HDPW HDPX HDQD HDQE HDQF HDQG HDQH	pCMVSPORT 3.0	LP08
HDPM HDPO HDPP HDPQ HDQP	pCMVSPORT 3.0	LP08
HMTM	PCR II	LP09
HLDX	pSPORT1	LP10
HMUB	pCMVSPORT 3.0	LP08
HULA HULC	pSPORT1	LP10
HFNA	pSPORT1	LP10
HKGA HKGB HKGC HKGD	pSPORT1	LP10
HISA HISB HISC HISD HISE	pSPORT1	LP10
HLSA	pSPORT1	LP10
HHEA HHEB HHEC HHED HHEE HHEF HHEG HHEH HHEI HHEJ	pCMVSPORT 3.0	LP08
HHEM HHEN HHEP HHEQ HHER HHET HHEU HHEV HHEW HHEX HHEY HHEZ	pCMVSPORT 3.0	LP08
HEQA	pCMVSPORT 3.0	LP08
HJMA HJMB	pCMVSPORT 3.0	LP08
HSWB	pCMVSPORT 3.0	LP08
HNTR HNTS HNTT	pSPORT1	NA
HEEA	Uni-ZAP XR	NA
HEGA	Uni-ZAP XR	NA
HSYA HSYB HSYD HSYE	pCMVSPORT 3.0	LP08
HLWA HLWB HLWC	pCMVSPORT 3.0	LP08
HRAA HRAB HRAC HRAE	pCMVSPORT 3.0	LP08
HTXJ HTXK HTXL HTXM HTXO HTXP HTXQ HTXR HTXS	Uni-ZAP XR	LP03
H6ED	Uni-ZAP XR	LP03
HAMF HAMG	pCMVSPORT 3.0	LP12
HAJA HAJB	pCMVSPORT 3.0	LP12
HDFU	pCMVSPORT 2.0	NA
HDHE	pCMVSPORT 2.0	NA
HLQD HLQE HLQF	Lamda ZAP II	LP13

2054

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HAPN HAPO HAPQ HAPR	Uni-ZAP XR	LP13
HWBA HWBB HWBC HWBD HWBE HWBF	pCMVSPORT 3.0	LP12
HWAA HWAB HWAC HWAD HWAG HWAI	pCMVSPORT 3.0	LP12
HYAA HYAB HYAC	pCMVSPORT 3.0	LP12
HWHG HWHH	pCMVSPORT 3.0	LP12
HWHP HWHQ	pCMVSPORT 3.0	LP12
HCWU	ZAP Express	LP13
HSIF HSIG	Uni-ZAP XR	PA005 Phage
HLTG HLTH HLTJ	Uni-ZAP XR	LP13
HARM HARN	pCMVSPORT 3.0	LP12
HBIM HBIN HBIO HBIP	pCMVSPORT 3.0	LP12
HSOB HSOD	Uni-ZAP XR	LP03
HCQC HCQD	Lambda ZAP II	LP01
HCNC HCND	Lambda ZAP II	LP01
HROB HROD	Uni-ZAP XR	LP03
HAHC	Uni-ZAP XR	LP13
HWDA	pCMVSPORT 3.0	LP12
HODE HODF HODG	Uni-ZAP XR	LP03
HTEL HTEP	Uni-ZAP XR	LP03
HBGM HBGN	Uni-ZAP XR	LP03
HTLG HTLH	Uni-ZAP XR	LP03
HHFJ HHFL HHFM	Uni-ZAP XR	LP03
HFKH HFKI HFKM	Uni-ZAP XR	LP03
HTPF HTPG HTPH HTPI	Uni-ZAP XR	LP03
HUVF HUVG HUVH	Uni-ZAP XR	LP03
HE2J HE2L HE2R HE2T	Uni-ZAP XR	LP04
HS2A	pSport1	LP16
HS2S	pSport1	LP16
HLQG	Lambda Zap II	LP01
HA5A HA5B	pSport1	LP16
HTTI HTTK	Uni-ZAP XR	LP03
HTAH	Uni-ZAP XR	LP03
HDDN	pSport1	LP22
HPCI	Lambda Zap- CMV XR	LP21
HPCR	Lambda Zap- CMV XR	LP22
HPMK HPML	Uni-ZAP XR	LP03
HHFO	Uni-ZAP XR	LP03
HAAA	pSport1	LP22
HOOH	pSport1	LP22
HIDA	pSport1	LP22
HNOA	pSport1	LP22

2055

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HUUA	pTrip1Ex2	LP22
HPDO	pSport1	PA005 DNA
HPCO	*pSport1	PA005 DNA
HOCM	pSport1	PA005 DNA
HNBT	pSport1	PA005 DNA
HBCJ	pSport1	PA005 DNA
HSAM	pSport1	PA005 DNA
HFXA HFXH	Lambda ZAP II	LP01
HMSA HMSC HMSD HMSF HMSG HMSH HMSI HMSJ	Uni-ZAP XR	LP03
HOSA HOSB HOSD HOSM HOSN HOSO HOSP	Uni ZAP XR	LP04
HEBA HEBB HEBF HEBG	Uni ZAP XR	NA
HAGB HAGD HAGE HAGF	Uni-ZAP XR	LP13
HSRA HSRB	Uni-ZAP XR	LP03
HPVA	Uni ZAP XR	PA005 Phage
HKIA	Uni ZAP XR	PA005 Phage
HKMA	Uni ZAP XR	NA
HSRF	Uni-ZAP XR	LP03
HSQD HSQF	Uni-ZAP XR	LP03
HSKE HSKZ	Uni-ZAP XR	LP03
HSLE HSLF HSLG HSLH	Uni-ZAP XR	LP03
HSDE HSDH	Uni-ZAP XR	LP03
HSXA HSXB HSXD	Uni-ZAP XR	LP04
HSXA HSHB	Uni-ZAP XR	LP13
HBXA HBXB HBXC	ZAP Express	LP13
HOUA HOUD	Uni-ZAP XR	LP04
HPWA HPWB HPWC	Uni-ZAP XR	LP13
HELB HELG HELH	Uni-ZAP XR	LP04
HEMF HEMG	Uni-ZAP XR	LP04
HBIB	Uni-ZAP XR	LP04
HFRA HFRB	Uni ZAP XR	PA005 Phage
HHSB HHSD	Uni-ZAP XR	LP04
HNGB HNGE HNGG HNGI	Uni-ZAP XR	LP04
HNHD HNHE HNHH	Uni-ZAP XR	LP04
HADB	Uni ZAP XR	NA
HSAX HSAW HSAX HSAZ	Uni-ZAP XR	LP04
HBMS HBMT HBMV HBMX	Uni-ZAP XR	LP04
HOBA	pBluescript	PA005 Phage
HOEE HOEF HOEK HOEL HOEM HOEN HOEO	Uni ZAP XR	PA005 Phage
HAIB HAIC HAID	Uni-ZAP XR	LP04
HTGA HTGB	Uni-ZAP XR	LP04
HEIB HEIC	Uni ZAP XR	NA

2056

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HMCD	Uni-ZAP XR	LP04
HPCA	Uni ZAP XR	NA
HPHA	Uni-ZAP XR	LP04
HPIA HPIC	Uni-ZAP XR	LP13
HPJA HPJB HPJC HPJE	Uni-ZAP XR	LP13
HFIA HFIB HFIC	pSport1	LP10
HFIH HFII HFIJ	pSport1	LP10
HFIU	pSport1	LP10
HSKX	pBluescript	LP03
HGCO	pSport1	NA
HMVA HMOV HMVC HMVD	pSport1	LP10
HOSE HOSF	Uni-ZAP XR	LP04
HNHN HNHO	Uni ZAP XR	LP04
HTGE HTGF	Uni-ZAP XR	LP04
HFPB HFPC HFPE HFPF HFPH HFPI HFPJ HFPK	Uni-ZAP XR	LP03
HFIX HFIY HFIZ	pSport1	LP10
HOHA HOHB HOHC HOHE	pCMVSPORT 2.0	LP07
HSDJ HSDK	Uni-ZAP XR	LP03
HFOX HFOY	pSport1	LP10
HMAH HMAJ HMAK HMAM	Uni-ZAP XR	LP04
HACB HACC	Uni-ZAP XR	LP04
HFXK	Lambda ZAP II	PA005 Phage
HFAT	Uni ZAP XR	PA005 Phage
HANG	pSport1	NA
HOUH	Uni ZAP XR	NA
HMCF HMCB HMCH HMCI	Uni-ZAP XR	LP13
HWLE HWLF HWLG HWLH HWMA	pSport1	LP14
HCRM HCRN HCRO HCRP HCRQ	pSport1	LP14
HWLI HWLJ HWLK HWLL HWMF	pSport1	LP14
HWLQ HWLR HWLU HWLV HWLW HWLX	pSport1	LP14
HBOD HBOE	pSport1	LP14
HBKD	pSport1	LP14
HWLA HWLC HWLD HWLP	pSport1	LP14
HWLM HWLN HWLO HWMB HWMC	pSport1	LP14
HVAA	pSport1	LP12
HBWC	ZAP express	LP13
HHSF HHSG	Uni ZAP XR	LP04
HSLJ	Uni ZAP XR	NA
HAQN	pSport1	LP14
HASM	pSport1	LP14
HCDM	pSport1	LP14
HFDM	pSport1	LP14
HGAM	pSport1	LP14
HHMM	pSport1	LP14
HAVM	pT-Adv	LP14
HAVT	pT-Adv	LP14
HHAT HHAU	pT-Adv	LP14
HUCN HUCO HUCP HUCQ	pSport1	LP20
HHAO	pCMVSPORT	LP15

2057

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	3.0	
HTFN	pSport1	LP16
HMSM HMSO HMSP	Uni ZAP XR	PA005 Phage
HEPN	pSport1	LP20
HPSN	pSport1	LP20
HNSA	pSport1	LP20
HNSM	pSport1	LP20
HOCN	pSport1	LP20
HOCT	pSport1	LP20
HLXN	pSport1	LP20
HTYN	pSport1	LP20
HZAA	pSport1	LP20
HINA	pSport1	LP16
HRMA	pSport1	LP16
HSKI HSKJ HSKK	pBluescript	LP03
HACA	Uni-ZAP XR	LP13
HFAA HFAC HFAD	Uni-ZAP XR	LP04
HFAM	Uni-ZAP XR	LP04
HMIA HMIB	Uni-ZAP XR	LP04
HILB HILC	pBluescript SK-	PA005 Phage
HPBE	pBluescript SK-	LP13
HIBC HIBE	Other	NA
HPDD	pBluescript SK-	NA
HSAA HSAB HSAC	pBluescript	LP05
HSBA	pBluescript SK-	LP13
HJAA HJAC	pBluescript SK-	LP13
HJBA HJBC	pBluescript SK-	LP13
HAFB	pBS	LP05
HTNA HTNB	pBluescript SK-	LP13
HONA	pBluescript	LP05
HBMA	pBluescript SK-	NA
HARA	pBluescript	LP05
H2CA	pBluescript SK-	NA
H2MA	pBluescript SK-	NA
H2MB H2MC	pBluescript SK-	PA005 Phage
H2CB	pBluescript SK-	PA005 Phage
HCYA	pBluescript SK-	NA
HCYB	pBluescript	PA005

2058

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	SK-	Phage
H2LA H2LB	pBluescript SK-	PA005 Phage

In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
10	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
15	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).)

Vector lafmid·BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from
5 Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in
10 Table 2 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 2 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA
15 clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that library in Table 2 and 9. First, a plasmid is directly isolated by screening the libraries using a polynucleotide probe corresponding to SEQ ID NO:X.

20 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ³²P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid
25 mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using
30 Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring

Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μ l of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A⁺ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of

the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template
5 for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

10 ***Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide***

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

15

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue (e.g., those shown in
20 Table 3 and 5) are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which are predicted to have significantly enhances expression in colon or colon cancer tissues were selected.

The original clone from which the specific EST sequence was generated, is obtained
25 from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of colon and/or colon cancer related clones. Housekeeping genes, maize genes, known tissue specific genes and known membranè localized class I genes are included on the filters as controls. These targets can be
30 used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial

expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Ampr), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

5 The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kanr). Transformants are identified by their ability to
10 grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical
15 density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar
20 Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

25 Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered
30 saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500

mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl.

5 The purified protein is stored at 4° C or frozen at -80° C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase
10 gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI,
15 BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated
20 according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

25

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture
30 is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by

weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then
5 mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is
10 discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous
15 stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is
20 loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM
30 NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH

6.5. Fractions are collected under constant A₂₈₀ monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus

Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce a colon or colon cancer related polypeptide, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and

Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by

Life Technologies Inc., Gaithersburg, page 9- 10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2.

If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ³⁵S-methionine and 5 µCi ³⁵S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV1, HIV1 and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and

pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., *J. Biol. Chem.* 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., *Biochem. et Biophys. Acta*, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., *Biotechnology* 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., *Biochem J.* 227:277-279 (1991); Bebbington et al., *Bio/Technology* 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell* 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, the vector does not need a second signal peptide.

Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with
5 appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction
10 enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a
15 group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different
20 concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for
25 instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins.
30 These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al.,

Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGGA
CACCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC
```

2073

AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC
5 GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:8555)

Example 10: Production of an Antibody from a Polypeptide

10

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available

from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human

PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10⁹ E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1%

2076

glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States

Biochemical). . Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2
5 are nick-translated with digoxigenin deoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium
10 iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using
15 the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for
25 a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal
30 or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

5 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 μ l of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

15 *Example 13: Formulation*

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By
20 therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given

continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see generally*, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the
5 Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid
10 content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

15 Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that
20 is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and
25 intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

30 The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,

succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention

include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21.

5 Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, 10 varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are 15 administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with 20 other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or 25 concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

30 In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited

to, soluble forms of TNF-alpha, lymphotoxin- alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha
5 (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International
10 Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with
15 antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and
20 COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir),
25 NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

30 In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not

limited to, TRIMETHOPRIM- SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the
5 Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

10 Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

15 In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids,
20 and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the
25 invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

30 In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid

derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not

limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL- 4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

5 ***Example 14: Method of Treating Decreased Levels of the Polypeptide***

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist
10 of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a colon or colon cancer related polypeptide in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising
15 administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

20

Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to
25 such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

30 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day

for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

5

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately
10 ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

15

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

20

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

25

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if
25 necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then
30 plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

2090

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce
5 infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer
10 cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.
15 Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via
25 homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is
30 not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous

polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains
5 distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the
10 appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

15 In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which
20 results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed
25 in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂
30 HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin.

The final cell suspension contains approximately 3×10^6 cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 $\mu\text{g/ml}$. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus,

heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal

2095

injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989));

electroporation of cells or embryos (Lo, 1983, Mol Cell Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration

of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect

cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and “knock-out” animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

***Example 21: Assays Detecting Stimulation or Inhibition of B cell
Proliferation and Differentiation***

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the

detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3 H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 22: T Cell Proliferation Assay

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ³H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10⁴/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 µl). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 µl of medium containing 0.5 uCi of ³H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ³H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6 /ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a

final concentration of 5 µg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

- 5 Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but
10 in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard
15 protocols provided with the kit.

- Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5 cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After
20 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The
25 absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

- The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
30 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 24: Biological Effects of Agonists or Antagonists of the Invention

Astrocyte and Neuronal Assays.

5 Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures
10 and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival
15 and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on
20 which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

25 Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate
30 for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is

added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released. Subsequently, MPP⁺ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2.5×10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology,

Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

5 An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity
10 of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 26: Rat Corneal Wound Healing Model

This animal model shows the effect of an agonist or antagonist of the invention on
15 neovascularization. The experimental protocol includes:

a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.

20 c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five
25 days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 27: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

30

A. Diabetic db+/db+ Mouse Model.

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the

rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned
5 perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence
10 of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue
15 control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon
20 cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

25 Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in*
30 *vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard

wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors*. 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors*. 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

2113

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

5

Example 28: Lymphadema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

15

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

20

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

25

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

30

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when
5 necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each
10 paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement,
15 a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief
20 halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated
25 prior to surgery and then at conclusion for total protein and Ca²⁺ comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal)
30 area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold

methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂. HUVECs are seeded in 96-well plates at concentrations of 1 x 10⁴ cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution

2117

of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 µl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: TAQMAN

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol
5 separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with
DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse
transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of
Taqman Buffer A (Perkin-Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM MgCl₂, 240 μM
each dNTP, 0.4 units RNase inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05%
10 gelatin, 0.3uM primers, 0.1uM probe, 0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units
Superscript II reverse transcriptase (Life Technologies). As a control for genomic
contamination, parallel reactions are setup without reverse transcriptase. The relative
abundance of (unknown) and 18S RNAs are assessed by using the Applied Biosystems Prism
7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. &
15 Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30
min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are
performed in triplicate.

Primers (f & r) and FRET probes sets are designed using Primer Express Software
(Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-
20 end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-
Elmer).

Example 31: Production Of Polypeptide of the Invention For High- Throughput Screening Assays

25

The following protocol produces a supernatant containing polypeptide of the present
invention to be tested. This supernatant can then be used in the Screening Assays described
in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml
30 in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working
solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at
RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel

pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

- 5 Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

- 10 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix.
- 15 Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

- Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on
- 20 PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

- 25 While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl_2 (anhyd); 0.00130 mg/L $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$; 0.050 mg/L of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$; 0.417 mg/L of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl_2 ; 48.84 mg/L of MgSO_4 ; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO_3 ; 62.50 mg/L of $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$; 71.02 mg/L of Na_2HPO_4 ; .4320 mg/L of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L
- 30

of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-
5 Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; and 99.65 mg/ml of L-
10 Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B12; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of
15 Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer)
20 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the
25 media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays
30 described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant.

Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 32: Construction of GAS Reporter Construct

5

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

10

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

15

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

20

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO: 8556)).

25

30

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is

encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the
5 Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

2123

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>			<u>STATS GAS(elements) or ISRE</u>	
			<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g (IRF1>Lys6>IFP)		+	+	-	1	GAS
	IL-10	+	?	?	-	1,3	
10	<u>gp130 family</u>						
	IL-6 (Pleiotrohic) (IRF1>Lys6>IFP)	+	+	+	?	1,3	GAS
	IL-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
15	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
20	<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid) >>Ly6)(IgH)	-	+	-	+	6	GAS (IRF1 = IFP
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
25	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
	<u>gp140 family</u>						
30	IL-3 (myeloid) (IRF1>IFP>>Ly6)	-	-	+	-	5	GAS
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS

2124

Growth hormone family

	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
5	EPO	?	-	+	-	5	GAS(B-
	CAS>IRF1=IFP>>Ly6)						

Receptor Tyrosine Kinases

10	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAAT
GATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:8557)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATT
TCCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCCTAACT
CCGCCCCATCCCGCCCCCTAACTCCGCCCCAGTTCGCCCCATTCTCCGCCCCATGGCTG
ACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTCC
AGAAGTAGTGAGGAGGCTTTTTTGGAGGCCCTAGGCTTTTGGAAAAAGCTT:3'
(SEQ ID NO:8559)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the

GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and
5 NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a
10 different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly,
15 other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 33: High-Throughput Screening Assay for T-cell Activity.

20 The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to
25 activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4⁺ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo
30 vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then

tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient
5 cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required
10 number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing
15 polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one
20 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly
25 from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each
30 well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated

cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 34: High-Throughput Screening Assay Identifying Myeloid Activity.

The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM MgCl_2 , and 675 uM CaCl_2 . Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium,

with a final density of 5×10^5 cells/ml. Plate 200 μ l cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 μ l of the supernatant prepared by the protocol described in Example 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 8560)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO: 8561)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified

2130

product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

Example 36: High-Throughput Screening Assay for T-cell Activity.

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of

agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I-KB is phosphorylated and degraded, causing NF-KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF-KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:8562), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTC
CATCCTGCCATCTCAATTAG:3' (SEQ ID NO:8563)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTG
CCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCC
CTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTAT
TTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGG

AGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:8564)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 33. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 37: Assay for SEAP Activity.

As a reporter molecule for the assays described in Examples 33-36, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min.

Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the

2133

results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11

2134

43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability.

5

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

10

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

15

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

20

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

25

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4

solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity.

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase

activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

5 Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which
10 can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers
15 #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

 To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced
20 by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate
25 is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is
30 removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

 Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg²⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity.

As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as

described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation.

This assay is based on the ability of human CD34+ to proliferate in the presence of

hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec

Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 µl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code sticker is affixed to the first plate for counting. The sealed plates are then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECR).

The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the

stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2 , 7% O_2 , and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or

agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation.

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2%

FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both
5 stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFα is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO₂ until day 5.

Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-
10 sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

15 On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay
Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super
20 Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on
25 paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 µl/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

30 A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of

polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells.

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The plate is read on a plate reader

at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

5

Example 46: Alamar Blue Endothelial Cells Proliferation Assay.

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from

oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction.

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final

concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 µC of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

5 Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

10 One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 48: Assays for Protease Activity.

15 The following assay may be used to assess protease activity of the colon or colon cancer related polypeptides of the invention.

20 Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacrylamide/0.1% SDS gels containing 1% gelatin or casein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis appear as clear areas against the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

25 Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mM NaPO₄, 1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control

30 Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983).

Example 49: Identifying Serine Protease Substrate Specificity.

Methods known in the art or described herein may be used to determine the substrate
5 specificity of the polypeptides of the present invention having serine protease activity. A
preferred method of determining substrate specificity is by the use of positional scanning
synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its
entirety).

Example 50: Ligand Binding Assays.

The following assay may be used to assess ligand binding activity of the colon or
colon cancer related polypeptides of the invention.

Ligand binding assays provide a direct method for ascertaining receptor
15 pharmacology and are adaptable to a high throughput format. The purified ligand for a colon
or colon cancer related polypeptide is radiolabeled to high specific activity (50-2000
Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling
does not diminish the activity of the ligand towards its colon or colon cancer related
polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides
20 are optimized to establish a workable signal to noise ratio for both membrane and whole cell
colon or colon cancer related polypeptide sources. For these assays, specific colon or colon
cancer related polypeptide binding is defined as total associated radioactivity minus the
radioactivity measured in the presence of an excess of unlabeled competing ligand. Where
possible, more than one competing ligand is used to define residual nonspecific binding.

Example 51: Functional Assay in Xenopus Oocytes.

Capped RNA transcripts from linearized plasmid templates encoding the colon or
colon cancer related antigen cDNAs of the invention are synthesized in vitro with RNA
30 polymerases in accordance with standard procedures. In vitro transcripts are suspended in
water at a final concentration of 0.2 mg/ml. Ovarian lobes are removed from adult female
toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocyte) are

injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response to colon cancer antigen or colon cancer antigen agonist exposure. Recordings are made in Ca²⁺ free Barth's medium at room temperature. The *Xenopus* system can be used to screen
5 known ligands and tissue/cell extracts for activating ligands.

Example 52: Microphysiometric Assays.

Activation of a wide variety of secondary messenger systems results in extrusion of
10 small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of a colon cancer antigen which is coupled to an energy
15 utilizing intracellular signaling pathway.

Example 53: Extract/Cell Supernatant Screening.

A large number of mammalian receptors exist for which there remains, as yet, no
20 cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the colon cancer antigen of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially
25 subfractionated until an activating ligand is isolated identified.

Example 54: Calcium and cAMP Functional Assays.

Seven transmembrane receptors which are expressed in HEK 293 cells have been
30 shown to be coupled functionally to activation of PLC and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM,

range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP
5 quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

Example 55: ATP-binding assay.

10 The following assay may be used to assess ATP-binding activity of the colon or colon cancer related polypeptides of the invention.

ATP-binding activity of the colon or colon cancer related polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5, 858, 719,
15 which is herein incorporated by reference in its entirety. Briefly, ATP-binding to colon or colon cancer related polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenylyl-5'-imidodiphosphate for 10 minutes at 4°C. A
20 mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP ($-^{32}\text{P}$ -ATP) (5 mCi/ μmol , ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition
25 of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular colon or colon cancer related polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenylyl-5'-imidodiphosphate provides a measure of ATP affinity to the colon or colon cancer related
30 polypeptides.

Example 56: Small Molecule***Screening.***

This invention is particularly useful for screening therapeutic compounds by using the colon or colon cancer related polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a colon or colon cancer related polypeptide of the invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the colon or colon cancer related polypeptides of the invention. These methods comprise contacting such an agent with a colon or colon cancer related polypeptide of the invention or a fragment thereof and assaying for the presence of a complex between the agent and the colon or colon cancer related polypeptides or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the colon or colon cancer related polypeptides of the invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the colon or colon cancer related polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with colon or colon cancer related polypeptides of the invention and washed. Bound colon or colon cancer related polypeptides are then detected by methods well known in the art. Purified colon or colon cancer related polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding colon or colon cancer related polypeptides of the invention specifically compete with a test compound for binding to the colon or colon cancer related polypeptides or fragments thereof. In this manner, the antibodies are used to
5 detect the presence of any peptide which shares one or more antigenic epitopes with a colon or colon cancer related polypeptides.

Example 57: Phosphorylation Assay.

10 In order to assay for phosphorylation activity of the colon or colon cancer related polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled ^{32}P -ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The colon
15 or colon cancer related polypeptides of the invention are incubated with the protein substrate, ^{32}P -ATP, and a kinase buffer. The ^{32}P incorporated into the substrate is then separated from free ^{32}P -ATP by electrophoresis, and the incorporated ^{32}P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the colon or colon cancer related polypeptides of the invention.

20
Example 58: Detection of Phosphorylation Activity (Activation) of Colon or Colon Cancer Related Polypeptides of the Invention in the Presence of Colon or Colon Cancer Related Polypeptides Ligands.

25 Methods known in the art or described herein may be used to determine the phosphorylation activity of the colon or colon cancer related polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

30 ***Example 59: Identification Of Signal Transduction Proteins That Interact With Colon or Colon Cancer Related Polypeptides Of The Present Invention.***

The inventive purified colon or colon cancer related polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled receptor PTK polypeptide is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, receptor PTK polypeptide is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the receptor PTK polypeptides, or specific phosphotyrosine-recognition domains thereof. The receptor PTK polypeptide interacting protein-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 60: IL-6 Bioassay.

To test the proliferative effects of the colon or colon cancer related polypeptides of the invention, the IL-6 Bioassay as described by Marz *et al.* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 95:3251-56 (1998), which is herein incorporated by reference). Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50 μ l, and 50 μ l of the IL-6-like polypeptide is added. After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are utilized. Enhanced proliferation in the test sample(s) relative to the negative control is indicative of proliferative effects mediated by colon or colon cancer related polypeptides of the invention.

Example 61: Support of Chicken Embryo Neuron Survival.

To test whether sympathetic neuronal cell viability is supported by the colon or colon cancer related polypeptides of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 96:11458-63 (1998), which is herein

incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM
5 Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO₂ in the presence of different concentrations of the inventive purified IL-6-like polypeptide, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mossmann, T., *J. Immunol. Methods*, 65:55-63 (1983)). Enhanced
10 neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the inventive purified IL-6-like polypeptide(s) to enhance the survival of neuronal cells.

Example 62: Assay for Phosphatase Activity.

15 The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the colon or colon cancer related polypeptides of the invention.

In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England
20 Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [γ -³²P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from ³²P-labeled MyBP.

Example 63: Interaction of Serine/Threonine Phosphatases with other Proteins.

The colon or colon cancer related polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 62 are research tools for the identification,
30 characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled colon or colon cancer related polypeptides of the invention is useful as a reagent for the purification of molecules with

which it interacts. In one embodiment of affinity purification, colon or colon cancer related polypeptides of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the colon or colon cancer related polypeptides of the invention. The colon or colon cancer related polypeptides of the invention-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 64: Assaying for Heparanase Activity.

In order to assay for heparanase activity of the colon or colon cancer related polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells (1×10^6 cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with ^{35}S -labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the colon or colon cancer related polypeptides of the invention in cleaving heparan sulfate.

Example 65: Immobilization of biomolecules.

This method provides a method for the stabilization of colon or colon cancer related polypeptides of the invention in non-host cell lipid bilayer constructs (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of colon or colon cancer related polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the

colon or colon cancer related polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of colon or colon cancer related polypeptides of the invention in washed membranes is incubated with 20 mM NaIO₄ and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl₂, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of U.S. Patent Application Serial No. 60/157,137 and 60/163,280 are also incorporated herein by reference in its entirety.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209059
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 209059**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209059**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209060
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209060**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209060**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209061
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer

ATCC Deposit No. 209061**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209061

Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209062</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p style="text-align: center;">For receiving Office use only</p> <p><input type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer</p>	<p style="text-align: center;">For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
---	--

ATCC Deposit No. 209062**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209062**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209063
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209063**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209063**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209064
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209064**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209064

Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution <i>(including postal code and country)</i> <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209065</u>
C. ADDITIONAL INDICATIONS <i>(leave blank if not applicable)</i> This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE <i>(if the indications are not for all designated States)</i> Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS <i>(leave blank if not applicable)</i> The indications listed below will be submitted to the International Bureau later <i>(specify the general nature of the indications e.g., "Accession Number of Deposit")</i>	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209065**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209065**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 *bis*)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209066
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209066**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209066**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

2182

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209067**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209067**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209068
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
---	--

ATCC Deposit No. 209068**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209068**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 *bis*)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209069
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 209069**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209069**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209579
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 209579**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209579**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 *bis*)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209578
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 209578**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209578**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application
Authorized officer

For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

ATCC Deposit No. 203067**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203067**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203068
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 203068**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203068**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>01 February 1999</u>	Accession Number <u>203609</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 203609**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203609**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 01 February 1999	Accession Number 203610
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer

ATCC Deposit No. 203610**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203610**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 17 November 1998	Accession Number 203485
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. 203485**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203485**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

2212

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
---	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 *bis*)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution <i>(including postal code and country)</i> <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>18 June 1999</u>	Accession Number <u>PTA-252</u>
C. ADDITIONAL INDICATIONS <i>(leave blank if not applicable)</i> This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE <i>(if the indications are not for all designated States)</i>	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS <i>(leave blank if not applicable)</i>	
The indications listed below will be submitted to the International Bureau later <i>(specify the general nature of the indications e.g., "Accession Number of Deposit")</i>	

<p style="text-align: center;">For receiving Office use only</p> <p><input type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer</p>	<p style="text-align: center;">For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
---	--

ATCC Deposit No. PTA-252**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-252**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-253
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. PTA-253**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-253**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 28 October 1999	Accession Number PTA-881
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. PTA-881**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-881
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
--	----------	-------------------------------	------------

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution <i>(including postal code and country)</i> <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>28 October 1999</u>	Accession Number <u>PTA-882</u>
C. ADDITIONAL INDICATIONS <i>(leave blank if not applicable)</i> This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE <i>(if the indications are not for all designated States)</i>	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS <i>(leave blank if not applicable)</i>	
The indications listed below will be submitted to the International Bureau later <i>(specify the general nature of the indications e.g., "Accession Number of Deposit")</i> 	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
--	---

ATCC Deposit No. PTA-882**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-882**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y, which is hybridizable to SEQ ID NO:X.

2225

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- (a) a polypeptide fragment of SEQ ID NO:Y;
- (b) a polypeptide fragment of SEQ ID NO:Y, having biological activity;
- (c) a polypeptide domain of SEQ ID NO:Y;
- (d) a polypeptide epitope of SEQ ID NO:Y;
- (e) a full length protein of SEQ ID NO:Y;
- (f) a variant of SEQ ID NO:Y;
- (g) an allelic variant of SEQ ID NO:Y; or
- (h) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

2227

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

SEQUENCE LISTING

<110> Birse et. al.

<120> Colon and Colon Cancer Associated Polynucleotides and Polypeptides

<130> PA005PCT

<140> Unassigned

<141> September 28, 2000

<150> 60/157,137

<151> September 29, 1999

<150> 60/163,280

<151> November 3, 1999

<160> 8564

<170> PatentIn Ver. 2.0

<210> 1

<211> 407

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (30)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (386)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (399)

<223> n equals a,t,g, or c

<400> 1

ggaacaagaa gaaagacaac catctcctgn aacctgtgca agaaaatgct aacagtgggtt 60
actatgaagc tcaccctgtg actaatggca tagaggagcc ttggaagaa tcctctcatg 120
aacctgaacc tgagccagaa tctgaaacaa agactgaaga gctgaaacca caagtggagg 180
agaagaactt agaagaacta gaggagaaat ctactactcc tcctccggca gaacctgttt 240

2

```

ctctgccaca agaaccacca aagccaagag tctgangctaa accagaagtt caatctcagc 300
cacctcgtgt gcgtggaaca acgacctaga gaacgacctg gttttcctcc tagaggacca 360
agaccaggca gaggagatat ggaacngaat ggactctgna caaccgt 407

```

```

<210> 2
<211> 413
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (373)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (380)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (396)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (407)
<223> n equals a,t,g, or c

```

```

<400> 2
gaattcggca cgagggtttt atgggcaaca gccatataca gtctacttcc tatctattgt 60
gaagttgttg ttgaggattt cctgtattat ttcactctgc attcatgtct cagttacctt 120
tgatccctag caaactgtcc caagtggaat ggcctaacct aggaatgatg tattatttct 180
tacagtccctg tgactgtctg ggcggtcctt ttgctaactt ccccgaggct cactgtgtgc 240
ttgtgggtcaa gtgatagcag cgttggctgg ctgggtccmag gtgggcctca cgtgtcctat 300
agtatttgct agctattgtc tgggggctcc tcaactcttc cacatgcccc agtaagcata 360
gaccagttcc ctnacaccan ggtgggtctc aggggnagca ttccaanagg gga 413

```

```

<210> 3
<211> 474
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

```

```

<400> 3
gacgggaatt tgatggaaaa ccaggacttg ctgggctcgc aacacctcca cctccccctc 60
cacaccagag gcactctgcac ctccactgcc cagcaaaact ccgcctcctc cccctccaaa 120

```


3

```

gacaactcgc aagcagacat cgggtggactc cgggatcgtk cagtgcgctc gcaaggctct 180
ctggaaagag tgtgtgccc ctccccatct ccatgccctc tccttctgtg tcccctgagt 240
ctgctgttta cctcattggg cctgtgatgt taacatttmg tgcgactgct ttttcttcaa 300
aggagttcag ttctcaccat ggagtgagtg gnccttttagc gtcatggagc aagggtgggtc 360
tgggaggtag atatgggtcc gggatgtgct atcgtagtta tcagarttgg gggcctctga 420
gtgtgtctgg ctctgagaga gtctgagtct tgcccaaaca ttctttcttt ttgg 474

```

<210> 4

<211> 1843

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (877)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1431)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1458)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1463)

<223> n equals a,t,g, or c

<400> 4

```

agaccttaac agacacctca ccaaagnagg tatacagatg gatacgcata tgaagagatg 60
ytcgacwtca tatgtcwtca agaaaatgca aattaaaata atgagatacc gctacatata 120
cattagaatg sccaaaaatcc aaagcactga caacaccgta tgctagttag gatgtggagc 180
aacagaaaact acttttcattg atggtggggac tgagaaacgg tatagccgct ttggaaaaca 240
gtttacaaaaa ctaaacatac tgttttcaac tccattggga gcataattat agttttattac 300
aggtagtwta attcagcagt tgcacacctt gttattttacc caatggagtt gaaagcttat 360
gtccacacgt aatgtgcaca taaatgttta cagagcttta ttcctaatac ccaaatttta 420
gaatcaaaaca agatgttctt cagcaggtaa atggataaac tgtgtacata cagacaatgg 480
aatattatgc agtgctaaaaa gaaatgagct gtcaagccat aaaaggacaa gaaggaaaaat 540
taaattgcattg ttactaaatg aaaaaaggcc atctgaaaag tctatatact gtatgattgc 600
aactatatga cattctgaaa aaggcaaaac tatggagaca gtaaaagatt agtggtttgc 660
aggaattggg gaagggggagg gacaaagaga gcacaaaata ttttttagtac agtaaaaccc 720
acgcgtccgc ggacgcgtgg gttttactgt actaaaaata ttttgtgctc tctttgtccc 780

```

4

```

tcccccttccc caattcctga caaccactaa tcttttactg tctccatagt tttgcctttt 840
tcagaatgtc atatagttgc aatcatacag tatatanact tttcagatgg cctttttcat 900
ttagtaacat gcatttaatt ttccttcttg tctttttatg gcttgacagc tcatttcttt 960
tagcactgca taatattcca ttgtctggat gtacacagtt tatccattta cctgctgaag 1020
aacatcttgt ttgattctaa aatttggtga ttaggaataa agcttctgta aacatttatg 1080
tgcacattac gtgtggacat aagctttcaa ctccattggg taaataacaa ggtgtgcaac 1140
tgctgaatta tactacctgt aataaactat aattatgctc ccaatggagt tgaaaacagt 1200
atgttttagtt ttgtaaactg ttttccaaag cggctatacc gtttctcagt cccaccatca 1260
atgaagtagt ttctgttgct ccacatcctc actagcatac ggtgttgta gtgctttgga 1320
ttttggccat tctaattggat atgtagcggg atctcattat tttaatttgc attttcttga 1380
tgacatatga tgcgagcat ctcttcatat gcgtatccat ctgtatacct nctttggtga 1440
ggtgtctgtt aaggtctntg atncatttta atgcttcttt gttaggggta gatacatgta 1500
aaggatatgt cttcttggag aattgactcc tttatcctta tataataatc ctctttgttc 1560
cttgtaactt gcattgctgt gcaatttgct ctttctgaaa ttagcacaat tgacccttga 1620
atgacatgga ggtagggggc acaaatgaaa atctgtgtat aactttttat tcactataa 1680
cttaactttt aaacccattt aacctcccc caaaattcag gaataataac acaccgacc 1740
acaccgctta caaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1843

```

<210> 5

<211> 471

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (161)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (428)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<400> 5

```

ggaagaagcc cagaggttgt gccaggggc agaaatcatt gcctagtgtt caccggctga 60
ctctcaactg accattccca tgtggacagg ccttaatact gtgagaggat ccttgctctg 120
ctggcagttt cccactccta tgcactttca caggaactag naaaactatt cttaaaccaa 180
aaataccatc cgtgttgacc catgttgcag agcccttact taaatccttc actggtgtat 240
gaatactttg tcataatgct gctttgctgg gtagttagct cttatttttc actgggggtc 300
agctataact aaaaactcaa gtgacatatt tcagttacca aagtggccag gaactttttg 360
cttttatgaa aatagattca tattgtattt cccagtgtgt cttytatgtc tttgaatgtt 420
ttagaganaa gtctatgcct gtctaaaaat gaatccagtg ttgcctttct n 471

```

<210> 6

<211> 905

5

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (836)
<223> n equals a,t,g, or c

<400> 6
gtttctagatc gcgagcgggcc gccctttttt ttttttgatt tatatgaact tgcaaatacat 60
atatattaac cttttgttat gtggagattt tggacaggag gattgcttga ggccaggaat 120
tcaagaccag cctgggaaac aaagtgagac cctgtcttta caaaaaataa aaacaaaaat 180
ttaaaactgt ataatctgca ctttatgcta aactagctgt gctcttaaac tcaatttttt 240
cagctctaataaagggctta atttgataga attattctac gattaaattt tgaagactgt 300
tttcaactctc ctctgccgcc catagcaaga ctgcttccat agatttctca gaaccgtagc 360
cagttctggc tatttggtca agtctgggat ccctcttacc tgctattctg cagctgcttt 420
ctctgtctta catttttttg gccacgtcta atcttaaaga gtaaactcta cccttggttt 480
gcatagtgtg catgacaaaa ataacaagaa taatggtaat gatgaaaatg ataagagcaa 540
aatttgtgga gtgctttcca cattccaggt aatgtgtaac atacaattta attcttacag 600
cagtccttatg gagtgaaaat actattatga attcccgttt tacagatgaa agaatggagg 660
cacagaaaag ttacttgtct aagtaacagt ctatccttaa agtccacagt cttaccact 720
tggatttttc atagtggagg aaaatatccc agaaagttgc agtttcaatt aatcactgaa 780
ttgtagggtta atttaactat accagtgaag tgccactga gcagaaatat ttgggncaac 840
atgaagccca ctggactggg agcttttgtt ttagcataat gaacctgttt ccagcaagat 900
tttga 905

<210> 7
<211> 412
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (108)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (372)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (377)
<223> n equals a,t,g, or c

<400> 7
aattcggcac gaggaactt gctattccac ccacaccaag ttaaaaagga aaaaaaaaag 60
acttttcgcac aattgtttcc taactgataa cattgtacat tcttaggnga ttagtaattg 120
tgtgaaattt actcatactg tttctaagtt tttcagcata gtcattgcac ttcagcaggg 180
aatctgagta tactttacag acagagtga cttaaaagtt taatgtcaag agattatggc 240

6

```

ttaaataaat tagtgtgtcc tataggggga aaaaaaccaa gaaaccacct tttaaaaaga 300
atgatatgcc atataccctt ggattttcat tttgcattat attgacgtgt ttttttgaag 360
ggaaaaaaag tnataanaat ctggatagtc taagactcca ctattttaaa ag 412

```

```

<210> 8
<211> 752
<212> DNA
<213> Homo sapiens

```

```

<400> 8
actgaacagt ggttaatcct gactctgttt ttgactgaca gttaacagtt acatgaacca 60
ttcatattac agctcttact taaatttgac caagccagga tataatctgtt aggccacatt 120
catttaggga tcatgttttc caaagcaggt ttgggcacaaa ttaatccaca ggactgaaag 180
gtatacatct gtgagttttg ttctcacttc cacctctaata ttgaagaaca ctttaattga 240
cacagaatac atttcacata ttttaacctct acaataagtt ctgacacatt ttccatgaaa 300
caaaccatcg ctatatccaa gataatgaac ctatctatca tactcccaaa ttcttctctkg 360
catcttttga atttctcact ctctctctct cctctccccg tcccatccca accactgac 420
tgctcaggca actaccaatc ttctttctgt cactatagat taatttgcatt ttttaaagaa 480
atttacatac atggaacatc acatcatcta tgctttgtag tatgactcct gtcactcagt 540
acaattatct tgagattcat ttatgttawt gtatgtatca atagtccatc ccttttattg 600
gtaagtaaca tttttttgta taggtatacc atgatttggt gatgaacaaa tttacctggt 660
gatgaacatt tacgttggtt ccaagatttt tgctattgaa aataaagttt ttatgaatat 720
ttatatatat aaaaaaaaaa aaaaaaactc ga 752

```

```

<210> 9
<211> 642
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (613)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (622)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (635)
<223> n equals a,t,g, or c

```

```

<400> 9
ggcagagggtg ctactggaag caatacgaaa aggtattcag ctacgcaaag tagaagagca 60
gcggtgaacag gaagctaagc atgaacgcac tgaaaacgat gttgccacca tctgtctctg 120
ccgtattgct gttgaatata gtgattcggga agatgattca gaatttgatg aagtagattg 180
gttgaggtaa gaaaaatgca ttgataaata ttacaaaact gaatgcaaat gtccttttgtg 240
gtgcttggtc cttgaaaatg tttgggtcatt ctagtgtttt gctttctttt ccttataata 300
aatgaccctt ttcttcata acttttgatt tctaaggaaa atattagcat acatttcaaa 360

```

```

ctaaatgttt tacagtggct tatctttttt ttccccctga aaagactaat ttgggtcaa 420
aaaccactaa gtattaagca tgggacagct gttgttagga gtagccagat tcagtttttt 480
ggatatatct taattgtgta ctttgtggaa ttttaaattt aaaggaaagg caactggaaa 540
ttggaaatcy tgaggggcag ctgtatctac taatgaggcc ttattccctt tcccggatgt 600
tttaaaggag ggnacactgc cntggattat acggnacac cc 642

```

<210> 10

<211> 211

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (210)

<223> n equals a,t,g, or c

<400> 10

```

tctttttctc tcccactttt tcatattcct ctttttcatt tttgcctttc cgtttctgtc 60
tatgatgtag gcttctgagg agaaccmaga agcttggtct tagtggtaga atgacagrac 120
ttagggatcc cttgcaggct agaacaaagt tctgaccctt agaccaaattc tttatgttaa 180
gaagttttcc agaattcaaa aaaaaaaaaan t 211

```

<210> 11

<211> 532

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (515)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (517)

<223> n equals a,t,g, or c

<400> 11

```

taagagatca aagcttataa ttttcttttt taatttttga aggagggatc aactccagtt 60
tccaatgtct atgtgtctat gtgtgtatgt gccatacata tgtattcaca tgaagaccgg 120
catggccaag ttctgctgga ggagcactca agtgtgacga gcagggccac tggaccctgc 180
agggtctgtg tgatatatag gcagctttgg aggtggaact ctattttcac acttttctat 240
ggagccttcc gagtcccagg ttttcacttg aggtgtctct tctggatggc ggttttcaga 300
cctccattaa catccctacc cagcattctg tacttcgggg gccttctctc ttgttataaa 360
actttttacc aagtgaacaa tcgataccac ctttgtttcc attctcactg gtgtaaatac 420
tgagtactaa ctgagaattt tgactttgca ttctgtcgga atacttgtgt tcaataaaaa 480
ttgaaagaaa aaagctaaaa aaaaaaaaaa aaaancncga gggggggccc gg 532

```

<210> 12

<211> 1120

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (711)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (946)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (987)

<223> n equals a,t,g, or c

<400> 12

```
cataaacatt gatgttgggt caatcatgtt ctcaatgtat ttaaccatgt gttttttaaat 60
tttttaattt agttatcaaa ttgagaatct gatggtatgg cattaatcac cttgaggaag 120
aacctttatc gttttatctga ttttcagatg catagagctc tggctgcttt aaaaaataaa 180
cctctaaatc atgttcacaa ggtagtcaag gagcgtctgt gcccttgggt gtgttcacga 240
caacctgagc ctttcgggggt cagattccat catgcccatt gtaaaaagtt tcattcgaaa 300
aatggaaatg accttcatcc actcgggtgga ccagtgttct ctcaagtatc tgactgcgac 360
aggcttgaac aaaatgttaa aaatgaggag agtcagatgt ttacaggag actgagcaac 420
ttgacttcat cagaagaagt gctaagtttt ataagcacga tggaaaccct gcctgacact 480
atggcgagcag gagctttaca acggatttgt gaagtggaaa aaaaggatgg tgatcaaggg 540
ctgccaaaag raatactgga gaatagcatc tttcaagctt tatgctttca gtttgaaaag 600
gagccctcac agctgtcaaa cactagttaa gtgactgctt tkcaagctct gattctgttg 660
catgtggatc ctcaaagtag cctgttgctg aacctggtgg cagaatgcaa naatcgtctc 720
agaaaagggtg gcatggaagt tgcgaatctt tgtattcttg gggaaagtct gattacactg 780
cacagttcag gttgtgtgac actagaactc attataaatc aacttcaagg tgaaaaattg 840
gaaacattta ccccgaggga tattgtggcc ctttatagaa tcttgagggc atgtactgaa 900
aaagtggatg aacaccaaac attttttaaat aagataaaca actttncctt atcaatagtt 960
tccaacctga gtcctaaatt gattagncaa atgctcactg ccctgggtgg tcttgatcaa 1020
agtcaagcat ttcctctgat tataaaattg ggcaaaatat gtcgtgaggc atgtcccaca 1080
tttcaactta cgaggagctt aggagagtct tttgaggcgt 1120
```

<210> 13

<211> 600

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (571)

<223> n equals a,t,g, or c

<400> 13

```
ctagatcgtc agggaggaag ggtcagttgg gtgcctgttt ttctgttttn agtcctttaa 60
aatgagtaga agcaacctgt taccctggaa agagcactgg acatagacct agtgctgcgt 120
gatgttgagc acgtttcttc ttccctttga gtcccagttt cccttttggg tacaggggga 180
tagtagcccc cagggatcat gtgaaagtga gaaagccctt ttcacactgt ggagcgggtgc 240
agatgtggga aacctcaaa atggttgccc attttaaatc ctttcacttc tcactctctc 300
ttcttctctc ccttctgccc tgacgtagcc atggttgggt gggtagaggc agaagaaact 360
gcctccgmaa gaggtagcag ccgctcaggt ggctctgctg gcacggagc ccacagaagt 420
gaggagtggc cgatggamct gccctccaaa tgtgcctgac tctgggtctt gctgtcactg 480
ggatttcctg ggcattggcag acagaaagaa agatagtttg accaagtcgt aggaagcttg 540
attccagcgg gtaaaaaagg gggcagggaa ntcgtccctt ttattttttg ccttcaggag 600
```

<210> 14

<211> 807

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (773)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (786)

<223> n equals a,t,g, or c

<400> 14

```
caattaaggg tgtacaaatt ataataatgc atctctatct tcatactttg aatggcaaac 60
gctattttatg cataaatatt ttcattttta gtaatatatg aagtgtaaat actcgatata 120
taagtataga ttttaaagat atgggacttt attttcacat aagtcaatag atgtttctct 180
agaacaaaaat atttagtaaa gctttataaa ttatattaaa aggaagcggg gaacatgtat 240
tttttaacat agaacagaag tgacttcatt ctttttagac atcagaaatg ttaaagttga 300
ttcccaatat ttgttgact tttttgtagc aaatgttaaa aatcacgagt taccatgtat 360
agaatgtgga ctgtcatgtt gatatcattg tacagtgata agccattttw atctgtatac 420
atttcaccaa tttattaaca ggttgaatat ttgtttcttt ttagaacatt ttattttatac 480
tgtgaagact ttgttatacc ttatttgcta caacatagat catatcattg ctactttgac 540
ttagcatttg catcataaac ataattatga tgtttttttc atgctccttc caggggctca 600
gtcacttgaa gaaactgttg ctaaccaagc tcttgactct gtttccctta atgatacaag 660
tctctgtacc agcgctttat gttaattacc aaaactctcc tgcacagag catgatatct 720
ataataggag atactgsaat aaaatgrttw ggctgtaaaa atttggaggc acnaattttc 780
caattncaat ggcaaattgg catggtg 807
```

<210> 15

<211> 416

<212> DNA

<213> Homo sapiens

<220>

10

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<400> 15

```
ngttttggga ttattataag ttcttgtgtc ttaaggccat ctgcttttat atccagtgat 60
gtgggatttt aatcagccat taattaggta agcattcact ttgaggacaa tattctgttt 120
tatcttgggt agcatggaca gtttgtcaca gaaataagtt ccctattcaa acttggaatt 180
agctgattca gagtaacata ttaataatat aaaaatggcc ataccctttt atggcgtaac 240
attatttcta ggtattgttt ctaaggaaat aattttaaat attgggaaaa aatattttta 300
caatttacag tctgtctgac atttggtaaa tagctaattg tgatatattc atattaggag 360
ataggggtgca gccactaaaa tgattttgaa gtattgtcca ttagtaatgg taattt 416
```

<210> 16

<211> 752

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (40)

<223> n equals a,t,g, or c

<400> 16

```
ggcctgggct ccttccgaat ggtgggcgct ctgagccagn ttctgaggag gagtcggagg 60
aggagcctga atgtttggag atagacttca agtcccggac cttatccgtg cgccgcttcg 120
gtttgcaggt gacctttgcg tgcgggcgcc cttctgatt gacctgatg agctgtagct 180
ctgatggccc ctccctcggg aatgattagg gtgacggctg kccggggctc gttcgagtgg 240
cgcccggccg gtggtgacce gaacaggaga gcgggacggc gaccattctc tcgggagggg 300
cccatytgga gaaagtccct tcgcttgggt aaactaggag ggcgatagca ccggccctac 360
tgcgacgatg acaaagtaca acacaccgtc tggcgcgaa gagatgctcg agaacccttt 420
gctgttggtt tttttcgcgt gtccctccga accaagggaa atgcggctct gtgggttctg 480
ttaacgtcag catttaataa gtgaactcta aatgcattgc cccttatggg tgcgctggcc 540
tcctgagttg actcagctct tgcaacgtag ctagttgata accctcgaaa tatagcgaat 600
tgagatgtgc tatattgtaa aatacgggac ttagtacgaa aaaactgatg taaaaattat 660
ctcaatactt tttaatactg attacatgtt ggaatataat gttttgcata tattgggtca 720
aataaaaatg ttattaattt caaaaaaaaa aa 752
```

<210> 17

<211> 481

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (442)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (447)

<223> n equals a,t,g, or c

$\langle 220 \rangle$

<221> misc feature

<222> (448)

<223> n equals a,t,g, or c

<400> 17

ggcagcagatt	tcaaaccaac	actgaaattc	tgtggcatca	catatatattg	gccttgatgt	60
catgacagak	caaaatcatt	tgatatccct	ttctccattc	taggtttttc	tttttttcag	120
taactgattt	accttgatca	cttttcaact	tccatattct	tcatatagta	aaaggcaaag	180
tgttgaagat	actacggtgt	ggtagtagtt	gaaaattatt	gccgtcatta	tttacatact	240
taagacatat	tagcaagttg	atccaaaatg	ggaggcctta	tagatgtgct	tgggggaaaa	300
tgaaggggag	aaagtagcca	tacaggagtt	caaagaattc	catgcccttc	agattagccc	360
attaccagaa	acatcatgaa	agtattttta	aaactaatta	tttactacag	tgtattttcac	420
ttgtcttgty	tgtctgaaca	cnagganngc	taaattagca	agttttttta	ggagggtattt	480
t						481

<210> 18

<211> 912

<212> DNA

<213> Homo sapiens

 $\langle 220 \rangle$

<221> misc feature

<222> (875)

<223> n equals a,t,g, or c

 $\langle 220 \rangle$

<221> misc feature

<222> (881)

<223> n equals a, t, g, or c

<400> 18

aattcggcac	aggatcagac	tctcttttcaa	ctgtctctccc	ctccaagcag	accacctgtc	60
cccttctatc	ccagctcaga	gcagctgacc	caactcagaa	tctcttttcc	acaggatgaa	120
gtgcctttttg	aatgttattt	taagccgaga	gttaattttt	ctacacaaca	tattttccaga	180
catctttttag	tctttttattg	tcttagatac	tataagaaga	tgaacatgac	aatttttctag	240
aacctggtag	cgtgtgtgtg	tgtggcgggg	ggtgctgagg	gaggggagtg	agtcacagga	300
gcctgtcccc	caacaggtgt	gactgctctg	acaacctgtg	gcattgctgca	gggtcaggct	360
cctgatagga	ggatttcattg	actatgtcat	tgtctccact	cattttttgac	ccagttttgga	420
atgtatctgc	aattgtgtgg	ctcaacactt	taggaacaaa	tagattattt	tatattatta	480
tttctgatgg	tgacaagttt	gtcttgagg	cacattttct	ccttgaaaag	tgacatcctg	540
tcactttctgc	tctcacacta	ctgccataca	tttgtgtttt	ttgttgttat	tgtttgggta	600
gagcagttac	aagaaaccct	aaaacccttg	gatataaaaag	aaatctgttt	attgattttt	660
aaatcttttc	tttccaaaag	ctgggataca	catgggagct	gtttggggaa	ttttccttgc	720
tgctaccgcg	ctgccaccaa	atgggaattg	accaggcggg	ctgttttacac	tgttttctttg	780
gccactgtgg	ccyatggctc	aggaatatgg	ctcactggct	aaggcttacc	aaactcgggg	840
acaggggggtc	agggaaacag	gaggggtgtt	ccccntcccc	nttggcaggc	cttcccaccc	900
acctggttaa	cc					912

12

<210> 19
 <211> 507
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (489)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (492)
 <223> n equals a,t,g, or c

<400> 19
 ggatacatag gaagttgacc tcgggggtatc atggagagtg tccctcctag tggctggagg 60
 tagggacagt tggttgtggg gctggagaga ggttgtgggg aggaagcgag gatgcgtgcc 120
 tgccactagg atctgcatcc ccgagcccaa gccaggaggg atttccctta ggcaacacca 180
 tcccaggagg atctgccaca atttgcgttt cacagctraa gacgccgagg cttagagagc 240
 tcgacctcct caagggtcaca ccactgggta aatagaggga tgcagactca ggttttgcta 300
 tgtgtctaca tttcaacttt atgcttaaca tgaatggaaa aatatgaaag taaatagtga 360
 aaagggtgagt tatgagctta gattacctag attattccag tatcccatgg aagctgagga 420
 cttattccgc tttccacacc gaacactaaa tgtggaccag tatcaagaac cctcctgtcc 480
 ccacgcagnt anaaccaggt ggcttct 507

<210> 20
 <211> 410
 <212> DNA
 <213> Homo sapiens

<400> 20
 ggcagagcca aaagaggggtt cttggatctc acgcaacaaa gagttcgggg cgagtccata 60
 gagtaaagtg aaagcaagtt catcaagaaa gcaaaggaat aaagaatgcc tactccatag 120
 gcagagcagt ggcttttggt gctcagctgc ttgtacttgt tacttcttga gtatatgcta 180
 aacaagggat tgattactcc ttgttttagca gttttctggg aaaggagtgg gcaattccca 240
 gaactgaggg ttcctcccct ttttaagacc atattagggg gacttcctga tgttgccatg 300
 gcatttgtaa actgtcatgg cgctrtgggw gtgtctttta gcatgctaata gctttataat 360
 tagcgtataa tgagcagtga ggacaaccag aggtcactct tgtctgtgcc 410

<210> 21
 <211> 496
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (36)
 <223> n equals a,t,g, or c

<220>

13

<221> misc feature
 <222> (356)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (443)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (454)
 <223> n equals a,t,g, or c

<400> 21
 ggcacgaggg cacs mkcaaa ccttgtcttc cctctnctgt tgcacccctt ccctaccctt 60
 ccctcccagg tgctcggtac tttaccwagt ttctatatat cagtgtttta tgttggaatt 120
 tttccttggt tttattttac tagttggtaa accctgttta tgctgaaaca aataaggaaa 180
 tggatatatt gaccatatgt gttattcata gaagacagta tgatcaaatt tgccaaaaac 240
 aagcaaacaa aacttaattc ctgrgaagta tgccttattt ttattgatct gctttgtctt 300
 acaattaagg tccaagagct tggttaaact gtattatttg cctaagtata aaaganaact 360
 tgaactgcat tgcaatattg acgttcttta aaatgagaga cactgtcaag taatttaatt 420
 cagagatcag ccaccagatt tagnaatgcct atgnatgtgt gtgtgttggg agtgggtttt 480
 tccttttaaac caccca . 496

<210> 22
 <211> 363
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (313)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (333)
 <223> n equals a,t,g, or c

<400> 22
 ggcacgagta taaatgatgg tgtggatgtc agggtagagg aggagacaaa accacgatga 60
 cccctagctt tgtggcctga actgtgggtg gctgagggga tcgttaattg aatggggcag 120
 actgaggctt gtraggaaga tcagagtctg gttcttgaca tgagatgccc ttcaaacatc 180
 tcttcactca ggtgcaacta gggatacaga aacactgkat atttcaacag cagaaattga 240
 atggggggat tgatagcsct ggcgagggaa gcagctggta aagaagacag atggcacccct 300
 gagacagccc agnggtggaa taggaccccc agngtgcagg gattaaagtt ccatgggttg 360
 gtg 363

<210> 23
 <211> 239

14

<212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (238)
 <223> n equals a,t,g, or c

<400> 23
 ctcaggctgc tgcacgtggs catccgcac cggccttityt tcgacagttt gaccgtggag 60
 agcgcgggacc tgcagggctg ctgcttttgc gggcctggca gccccaccc gagaagatgg 120
 agttccggac ggcattctatc cgctctttg ggcacttaac aaggtctgcc acggagactg 180
 taaggacgtc ttcttgacc aagtgggtggg cgggctggcg cctgctgct gcacctgna 239

<210> 24
 <211> 461
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (426)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (428)
 <223> n equals a,t,g, or c

<400> 24
 aacaattaag tcttttaggaa tgtgtaacca gaactatggt agtattgctt ataaaacttt 60
 agtttaggttc aatatataca tatatacatc tctatatagg tatatagatt tgcattttgt 120
 cttgtaaaat tttatttgaa taaattcttc ctgtaggtaa tgggaaacaa aattaatagt 180
 tcatatgtca ctcatagcat ttctatattt gaaagtagcc caatataaaa cttttgattc 240
 taaaattaaa ccagcagcct attacaagca cattctttga ttgagtcatt gggtataaac 300
 ttactaaatg cagrgaagc agccaattta gggaaacttc tgagttggtg gggacactgt 360
 tggattaata atgtacggta tgaattaagt gatgccttaa cttggatttt acattttaag 420
 gttaangngg gggcatatgg tcagccaact tagggggcat t 461

<210> 25
 <211> 453
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (442)
 <223> n equals a,t,g, or c

<400> 25
 accagaccaa ccctatgaat ggctttcata taaacagggt gcagaattgt cggagtgcac 60

15

```

aggctcagca ctgatccaga agggcttcaa gactgcecca gatcagttca ttggcatctt 120
tgctcaaaat agacctgagt ggggtgattat tgaacaagga tgctttgctt attcgatggg 180
gatcgttcca ctttatgata cccttggaat tgaagccatc acgtacatag tcaacaaagc 240
tgaactctct ctgggtttttg ttgacaagcc agagaaggcc aaactcttat tagagggtgt 300
agaaaataag ttaataaccag gccttaaaat catagttgtc atggatgcct acggmagtaa 360
ctgggtggaac gaggccagag gtgtgggggtg gaagtcacca gcatgaaggc gatggaggac 420
ctgggaagag ccaacagacg gnagcccaag cct 453

```

```

<210> 26
<211> 1940
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (576)
<223> n equals a,t,g, or c

```

```

<400> 26
ggcagaggtc ctcagtgcag ggcaacagga ctttaggttc aagatggtga ctgcagccat 60
gctgctacag tgctgcccag tgcttgcceg gggccccaca agcctcctag gcaagggtgg 120
taagactcac cagtctcctgt ttggtatttg acgctgtccc atcctggcta cccaaggacc 180
aaactgttct caaatccacc ttaaggcaac aaaggctgga ggagattctc catcttgggc 240
gaagggccac tgctcccttca tgctgtcggg actccaggat gggaagagca agattgtgca 300
gaaggcagcc ccagaagtcc aggaagatgt gaaggctttc aagacagatc tgctagctc 360
cctgggtctca gtcagcctaa ggaagccatt ttccgggtccc caggagcagg agcagatctc 420
tgggaaggtc acacacctga ttcagaacaa tatgcctgga aactatgtct tcagttatga 480
ccagtttttc agggacaaga tcatggagaa gaaacaggat cacacctacc gtgtgttcaa 540
gactgtgaac cgctgggctg atgcataatc ctttgnccca acatttctct gaggcattctg 600
tggcctcaaa ggatgtgtcc gtctggtgta gtaatgatta cctggggcat gagccgacac 660
cctcaggtct tgcaagccac acaggagacc ctgcagcgtc atgggtgctgg agctgggtggc 720
acccgcaaca tctcaggcac cagtaagttt catgtggagc ttgagcagga gctggctgag 780
ctgcaccaga aggactcagc cctgctcttc tctcctgct ttgttgccaa tgactctact 840
ctcttcacct tggccaagat cctgccaggg tgcgagattt actcagacgc aggcaacct 900
gcttccatga tccaaggat cctgaacagt ggagcagcca agtttgtctt caggcacaat 960
gacctgacc acctaaagaa acttctagag aagtctaacc ctaagatacc caaaattgtg 1020
gcctttgaga ctgtccactc catggatggg gccatctgtc cctcgagga gttgtgtgat 1080
gtgtccacc agtatggggc cctgaccttc gtggatgagg tccatgctgt aggactgtat 1140
gggtcccggg gcgctgggat tggggagcgt gatggaatta tgcataagat tgacatcatc 1200
tctggaactc ttggcaaggc ctttggctgt gtgggcgggt acattgccag caccctgac 1260
ttggtggaca tgggtgcgtc ctatgctgca ggcttcatct ttaccacttc tctgcccccc 1320
atggtgctct ctggagctct agaatctgtg cggctgctca agggagagga gggccaagcc 1380
ctgaggcgag cccaccagcg caatgtcaag cacatgcgc actactcatg gacaggggccc 1440
ttcctgtcat cccctgcccc agccacatca tccccatccg ggtgggcaat gcagcactca 1500
acagcaagct ctgtgatctc ctgctctcca agcatggcat ctatgtgcag gccatcaact 1560
acccaactgt ccccggggt gaagagctcc tgcgcttggm accctcccc caccacagcc 1620
ctcagatgat ggaagatttt gtggagaagc tgctgctggc ttggactgcg gtggggctgc 1680
ccctccagga tgtgtctgtg gctgcctgca atttctgtcg ccgtcctgta cactttgagc 1740
tcatgagtga gtgggaacgt tctacttctg ggaacatggg gcccagtat gtcaccacct 1800
atgcctgaga agccagctgc ctaggattca cccccacct gcgcttcaact tgggtccagg 1860
cctactcctg tcttctgctt tgttgtgtgc ctctagctga attgagccta aaaataaagc 1920

```

acaaaccaca gcaaaaaaaaa

1940

<210> 27

<211> 864

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (552)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (773)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (856)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (863)

<223> n equals a,t,g, or c

<400> 27

tctaaatcca	ttacaaatct	gcttagcttc	taaatatttc	atcaatgagg	aaatcccagc	60
cctacaactt	cggaacagtg	aaatattagt	ccagggatcc	agtgagagac	acagaagtgc	120
tagaagccag	tgctcgtgaa	ctaaggagaa	aaagaacaga	caaggggaaca	gcctggacat	180
ggcatcagag	atccacatga	caggcccaat	gtgcctcatt	gagaacacta	atgggcgact	240
gatggcgaa	ccagaagctc	tgaagatcct	ttctgccatt	acacagccta	tggtggtggt	300
ggcaattgtg	ggcctctacc	gcacaggcaa	atcctacctg	atgaacaagc	tggtctggaaa	360
gaaaaagggc	ttctctcttg	gctccacggt	gcagtctcac	actaaaggar	tctggatgtg	420
gtgtgtgccc	cacccaaga	agccaggcca	catcctagtt	ctgctggaca	ccgaggggtct	480
gggagatgta	gagaaggggtg	acaaccagaa	tgactcctgg	atcttcgccc	tggtcggtcct	540
cctgarcagc	ancttctrtgt	acaatagcat	aggaaccatt	aaccagcagg	ccatggacca	600
actgcactat	caatctcggg	cctgaacctc	acctccaaaa	agaaagcgac	ttcagtagaa	660
agtgggggtca	gaaggaagag	tgtgggtcctg	gcccagctag	acaaaaagcg	ggatgacttt	720
tgtaaacaga	atcaggaagc	atcatcagat	cgttgtctcag	ctttacttca	ggncattttc	780
agtcctctag	aagaagaagt	gaagggcggg	gaatttttatt	tcgaaaacca	agggggggtaa	840
ccgtctctgt	tattcnagaa	agnt				864

<210> 28

<211> 703

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (549)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (612)

<223> n equals a,t,g, or c

<400> 28

```

gggtcgaccc acgcgtccgc caggagtagg tcctatcagt gcccccccag agtagagagc 60
aataagagcc cagcccagtg cagtccccgc tgtgttttcc tacctggtga tcagaagtgt 120
ctggtttget tggctgcccc tttgcctctt gagtgggcag ccctgggctt gggccccctcc 180
ctccggccct cagtgttggc tctgcagaag ctctgggggt cccttcaagt gcacgagggg 240
ttaggctget gtccctgagt cctccattct gtactggggg gctggctagg acctggggct 300
gtggcctctc agggggcagc ctctccatgg caggcatccc tgccttgggc tgccctcccc 360
cagacccctg accacccctt gggtcctgtc ccccaccaga gcccagctc ctgtctgtgg 420
gggagccatc acggtgttcg tgcagtccat agcgcttctc aatgtgtgtc acccggaacc 480
tgggagggga gggaacactg gggtttagga ccacaactca gaggctgctt ggccctcccc 540
tctgaccang cttatcctga gtttggtggc tacttccctc tggcctaagg taggggaggc 600
cttctcagat tntgggggca cattgtgtag cctgacttct gcaggagctc ccaattccag 660
gaaggaaaag agccaaggcc ccacttttgg ggatcagggg ggg 703

```

<210> 29

<211> 337

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (71)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (332)

<223> n equals a,t,g, or c

<400> 29

```

aggtgacact atagaaggta cgcctgcagg taccggatcc ggaattcccg ggtcgaccca 60
cgcgctccgca nttacattta tgttttagt tctaagtaag accctgagag attttcaaaa 120
aggaattaat gattattttt gtcttcccca ggattggaac gagttactat gctgtttctg 180
ggattgcata atgttcgtca gacctccatg ttccctcgtg atcccaaacy actcactcct 240
taaaattcaca ctttgccact taactccagt gtggatgaca gagcgagacc ctgcctcaaa 300
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nnccccc 337

```

<210> 30

18

<211> 631
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (524)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (608)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (615)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (630)
 <223> n equals a,t,g, or c

<400> 30
 agggaaactca ctgtgggtttt ratttgtatt tycttttttta agtgaaagca rgkttattaa 60
 gaaagcaaag gaataaagaa tggctattcc ataggcagag cccattgcc a ctcagctgct 120
 tatacttatt gttacttctt gattgtatgc taaacaaggg gtggattatt catgagtttt 180
 atgggaaagg ggtgggcagt atctggaact gagggtttct cccctttgta gaccatacag 240
 ggcaacttcc tgacgttgcc atggtatctg gaaactgtca tgggtgctggt ggaagtgtct 300
 tttagcatgc tgatgcatta taattagagt ataatgaata gtaaggacaa ccagagggtca 360
 ctttcatcgc catcttggtt ttggtcagct tctttactgc agcctgtttc atcattaagg 420
 tctttattac ctgtatcttg tgccgacctc ctgtctcacc ctgtgactta gaatgcctaa 480
 cctcctggga atgtagccca gtgggtctca gccttatttt actncacccc ctaattcaag 540
 atgggagttt ctctgggttt cagacaaccc ctggacatgt tttccccct ccctttttac 600
 agcagaancc ttaantccca acagtcgtan a 631

<210> 31
 <211> 571
 <212> DNA
 <213> Homo sapiens

<400> 31
 gaattcggca cgagtcccac cagcccccca aaaaacctct cagtagtttc tttcagtgtgta 60
 caaaatgatg agcatttttc tatgatgagg ttttaaccat tattcagggg ggtctttttgt 120
 ttttaaactct ttttttaact aataagattt acggtgtgta ttttatacag aaatgcatta 180
 taaatgtttt taattgtgtt ctgttttttg cagtctttta gtgccatgcc aattgttctt 240
 atattctata gaagtctcgt caaaatactc aacaggggaa taggcagcgg acagtcagaa 300
 tggttggaat tttggctttc taagaaaaac tttatttttg ataagcatgt ggtcagatca 360
 ttttgtgcat atgcagcctg gattggatgt taagtaaata cttgttcagt gccgggtacat 420
 ttactttaat ctgtttttat ttttgtcatg tagaatacta ctgtgggtcat cataatgtaa 480

19

tctattttctg tacctttttt tttttttttt acttttgaagt cttaaataaa atgtataata 540
ccccaaaaaa aaaaaaaaaa aaaaaaaaaa a 571

<210> 32
<211> 424
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (413)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (414)
<223> n equals a,t,g, or c

<400> 32
tttctaaaaa tcaggaaaat tagttactaa aaattgctga tcatttttgt ttcattatatt 60
ttgttattttc aaatgtataa gctctgggat tcttttttga gcaataccta caaagtcagg 120
caccagaatg tgccctcagag ctgtgacatt tcaacatgat ggtttttggtt tggtttggtt 180
ttgtgtcctt tttattttgca gtttttttctg ttgcaacaga aagtggcttg gaagtcttag 240
gtgggtatgta acaaattctt tttaaaaatt ttaaagcagt atttaagtat tcttaaatgt 300
gtaaattcat ttaatgtttt acttctaatt tcttgtatct tggctgtctg gttttattgc 360
attttttaaaa aaactgaacc attaagkaat tggaaatgaa tgaaggtgaa atnnctgaac 420
ctga 424

<210> 33
<211> 1626
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (525)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (542)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (562)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (607)

<223> n equals a,t,g, or c

<400> 33

```

ccacgcgtcc gacgcggcgc acgcggcagt cctgatggcc cggcatgggt taccgctgct 60
gcccctgctg tcgtctctgg tcggcgcggt gctcaagcta ggaaatggac aggctactag 120
catggtccaa ctgcaggggt ggagattcct gatgggaaca aattctccag acagcagaga 180
tggtgaaggg cctgtgcggg aggcgacagt gaaacccttt gccatcgaca tatttctctg 240
caccaacaaa gatttcaggg attttgtcag ggagaaaaag tatcggacag aagctgagat 300
gtttggatgg agctttgtct ttgaggactt tgtctctgat gagctgagaa acaaagccac 360
ccagccaatg aagtctgtac tctgggtggt tccagtggaa aaggcatttt ggaggcagcc 420
tgcaggtect ggctctggca tccgagagag actggagcac ccagtgttac acgtgagctg 480
gratgacgcc cgtgcctaata gtgcytkgsg ggggraaacg actgncccac sggagggaag 540
antggggagt ttttcgccc gnaggggggc ttgaarggtc caagtttacc ccatgggggg 600
aactggnttc cagccaaacc gcaccaacct gtggcagggg aagttcccca agggagacaa 660
agctgaggat ggcttccatg gagtctcccc agtgaatgct tccccgccc agaacaacta 720
cgggctctat gacctcctgg ggaacgtgtg ggagtggaca gcacacacgt accaggctgc 780
tgagcaggac atgcgcgtcc tccggggggc atcctggatc gacacagctg atggctctgc 840
caatcacccg gcccggtca ccaccaggat gggcaacact ccagattcag cctcagacaa 900
cctcggtttc cgctgtgctg cagacgcagg ccggccgcca ggggagctgt aagcagccgg 960
gtggtgacaa ggagaaaagc cttctagggg cactgtcatt ccctggccat gttgcaaaca 1020
gcgcaattcc aagctcgaga gcttcagcct caggaaagaa cttccccttc cctgtctccc 1080
atccctctgt ggcaggcgcc tctcaccagg gcaggagagg actcagcctc ctgtgttttg 1140
gagaaggggc ccaatgtgtg ttgacgatgg ctgggggcca ggtgtttctg ttagaggcca 1200
agtattattg acacaggatt gcaaacacac aaacaattgg aacagagcac tctgaaaggc 1260
cattttttta gcatttttaa atctattctc tcccccttc tccctggatg attcaggaag 1320
ctgmacattg tttcctcaag gcagaatatt cctgggttctg ttttctcagc cagttgtctgt 1380
ggaaggagaa tgctttcttt gtggcctcat ctgtggtttc gtgtccctct gaaggaaact 1440
agtttccact gtgtaacagg cagacatgta actattttaa gcacagttca gtcctaaaag 1500
ggtctgggag aaccagatga tgtactaggt gaagcattgc attgtgggaa tcacaaagca 1560
aatagtactc cagaaagacc ctgtctcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaa                                           1626

```

<210> 34

<211> 450

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (404)

<223> n equals a,t,g, or c

21

<220>

<221> misc feature

<222> (439)

<223> n equals a,t,g, or c

<400> 34

```

acccacgcgt ccgccggcgc ggtctatggc tgcgacttct ctaatgtctg ctttggtctg 60
ccggctgctg cagcccgcgc acagctgctc ctttcgcctt cgccctttcc acctcgcggc 120
agttcgrgga akctctccct aggtcagggt ggagtgcagt gctgcaatca cggcttactg 180
cagccttgac ctctggggct caagtgatec tcccacctca gcttaaataga agctgttgct 240
atctctggaa ggaaactggc ccagcagatc aagcaagaag tgcggcaaga ngtagaagat 300
ggggtgggct ccaggcaaca aacggccaca cctgaatgtt gatcccgggt tggcgaaaaa 360
tcctgcaag tcactcctaa tntcctccaa caaaaacaaa gggnaagttg caatttgttg 420
ggaaatccac cagttgaana acaatttttt 450

```

<210> 35

<211> 960

<212> DNA

<213> Homo sapiens

<400> 35

```

atTTTTTTTT tTTTTTTTTT tTTTTTTTaaa acaacttctc aaattttattt aactcatgtg 60
gttaacatgg tattgtataa aaagaaaaaa aaaacaccac tcaatactta ctaagccttg 120
cagacagctc agagttgagg cagcatattg ggcatagaga tcataggatt tgtattatcc 180
cttgcaagat ggaactccaa ccaacaccag aattttccaa ttcaaattca gtttttagtcg 240
agaccccgagc ataatttttta gaaaaaagat tggattgttg cttttctttt aattttccat 300
tcctattttag acaaattgacc agaggcaatg acaaaaagtaa ctgttttaaaa gggattttctc 360
tcagaagtt ttttctaaag gtttaagtcc aggttttcca tccttctctc catccttttt 420
catttttaaaa agaagggttt tggratwtgt caacctttac tcagcttgct atacaaagcc 480
actgcttttag tcctagacat aatgccagga ctcatctccc aaacttcttg tcttaataca 540
gttcattgctt gggttgctaaa gaagctcatg ttaatcccaa agtcagcaca atcccaacct 600
taaaaagcag acagcctgat tgcatactt acgacataca ccattcttgag gcaaaaagaag 660
ccagtcagac accccttgct tgcatactt gagacacatc agcagttgag cctgacccct 720
tcgcagagc tcactgtgca aaatccaccag cacaccactg caatccactg agctcaccgc 780
ctgtccagcc ataatggaag tcacttgaag gttatcattg taatagatga ttttccataa 840
gtaactaata aaaatgtttt ctttgatgtt tagacctact aacaattcag tctctccctc 900
tccatcctct cttaggggagc ctgtactttt aagcaaatag ggaagctaaa acctcgtgcc 960

```

<210> 36

<211> 530

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (78)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (362)

<223> n equals a,t,g, or c

<400> 36

```

taacaattca atatataatt acacaaataa ttttttaaata taatcaatag taaagactgt 60
tctgtggatg gtagtgtnta atacattttc tattttgtac agtgatttta ggccaaacag 120
ctgctgattt taagaaaaca aaaggcctga aaccgcgtctt cgtgtctcct cctccctcg 180
ccttcctcct tcctagctcc tctcctccag ggccagactg agcccagggt gatttcaggc 240
ggacaccaat agactccaca gcagctccag gagcccagac accggcggcc agaagcaagg 300
ctaggagctg ctgcagccat gtcggccctc agcctcctca ttctgggcct gctcacggca 360
knccacctgc cagctgtcag caaggcctgg ggaacttcag ccctggatgc agggccttat 420
cgcggtggcc gtgttcctgg tcctcgttgc aatcgctttt gcagtcaacc acttctggtg 480
ccaggaggag ccggagmtgg gagtccctggt ggggaacaga ttggaaggta 530

```

<210> 37

<211> 538

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (41)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (502)

<223> n equals a,t,g, or c

<400> 37

```

gccgcggcca cggggcgcag gggccatggt gcgcggcagg ntcttcgggc tctcgggtccg 60
ggacgtgcgc ttccccacgt cgcttggggg ccacggcgcg gacgccatgc acacggaccc 120
tgactactca gctgcctatg tcgtcataga aactgatgca gaagatggaa tcaaggggtg 180
tggaattacc ttactcttgg graaaggcac trwagttggt gtctgtsctg tgaatgccct 240
cgcccaccat gtgctcaaca aggacctcaa ggacattggt ggtgacttca gaggcttcta 300
taggcagctc acaagtgatg ggcagctcag atggattggt ccagaaaagg gcgtggtgca 360
cctggcgaca sggcgcgtct aaacgcgggtg tgggacttgt gggccaagca ggagggaaag 420
cctgtctgga attacttgtg gacatggatc ccaggacgct ggtatcctgc atagatttca 480
ggtacatcac tgatgtcctg antgaggagg atgccctaga aatactgcag aaagtcaa 538

```

<210> 38

<211> 1256

<212> DNA

<213> Homo sapiens

<400> 38

```

ggcacgagca ttaacaaaaa aatgtgcaaa cacactacta tgattttacca aaagactctc 60
tgcaagtggg aaatcattag ctctagtgtt gctcttttga acctcagggtc tttgggggaat 120
ggtgcagaat tagtattgct tccttctttc tgtgtgtgat aatgggtgggg gaaggctagt 180
accatctctg tcatacatca aattcccata tgtgaataaa tttatgtatt tttactgcac 240
tctttttata ggtttatcat tcctgcacca acaacgaatg ccattattaa aactttatag 300

```

23

```

aaagtctcaa tatatggcac agtgcttcat ttcttttttt catctagagt gccttagcca 360
ttcttggett tctgccgttc cacaaatagc aatgtaaatt tgtcagtata atagagaatc 420
cacttatatt tcttcaacag ctattgggaa tatgggtggg attacttcaa ctctatgtat 480
caatttgagg agaattgata tctttataag attaatccaa atcacagcat gtcaaaattt 540
ccttattagg gtagtttttaa tgccttcaa aaacactgta ttttcttcat atagatctaa 600
gaaaactttg gtgtttattc ctaagaaatt tatagttctt gttttgtaaa tgatatctat 660
tcttaagtta cacttaaact tatttgttgc tgtatataga aatggaattg acttctatgt 720
acagcagttg caaactgata ttcatatgca gaaagtgaaa ctagaccctt aatggataaa 780
agacttaaat gtaagacctg aaagtatgaa actactagaa gaaaacatat gggaaacact 840
tcagtatcct ggcctgggtg aagattttat ggagaaaacc tcaaaagcat aggcaacaaa 900
agcaaaaatg gacaaatagg attatatcaa actaaaaaga ttcagcacag taaaataaat 960
aatcwataga gtgaagagac aaccttcaga agatatttgc aaactattca tctgacaagg 1020
gattaatatt tagaacatac aaggacctca aacaactgag caacaacaac aaaaatatcc 1080
aattttaaaa atgggcgaaa gagccaaata aacatctctg aaaaccagac gcaagtggcc 1140
aacagg tataaaaaaa aaatgctgaa caccgcta atcatcaggaa atgcaaacca 1200
ataccacaat gagatattat ctcatwtggt ctattatcaa aaaaaaaaaa aaaaaa 1256

```

<210> 39

<211> 666

<212> DNA

<213> Homo sapiens

<400> 39

```

tggcacctgc aggactgcca agatctcctt ggcgctgcgg ggccattggc ggggatgggc 60
ggggggagggg ggcctcgacg gtttcccatc cccctctggc aaccctaate ttctttctcc 120
atctgggccc tggggcgtct tccaccaccc aggcgggatg ctttaaaaaa aattgctttt 180
taaagtgtct gtcgttgaaa gaaattagtc ttacccttga agtcargggc gcgtctctgc 240
aatacacatc ttgttaggga aagtgttcgg ctccagctak ggttctacaa ggcgtttctt 300
gttcaccgcc ggagggaagc aggtccgga gtgactgcct tctgaaagtc ggtcttgtaa 360
caattggatg ratgcctttg aagagccctt gtccctattc tatgcttgaa aacagcgtgc 420
agtcctaata ttcaagaacc acgaccacat aaaaacattg ctcccttctt gctgctttga 480
aaacgacccc taaattccgt gtagaagttg ccaggtcgtc ttgacgtaca cttcgtttgt 540
atgatgtttg tctgtcaaat actgtgatgg aagagtgtat gcgggggagg agcaggggat 600
ttttaaaarc attttccgk caccctagac tgggagatca tgttcttttc tgaaaaaaa 660
aaaaaa

```

<210> 40

<211> 1016

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<400> 40

```

ctggcnctgc atctcaaca tctcaaagg gtacaacttc tcccgggaga gcgtggagag 60
ccccgagcag aagggcctga cgtaccaccg catcgtagag gctttccggg ttgcctacgc 120
caagaggacc ctgcttgggg accccaagtt tgtggatgtg actgaggtgg tccgcaacat 180
gacctccgag ttcttcgctg ccagctccg ggcccagatc tctgacgaca ccaactaccc 240

```

24

```

gatctcctac tacaagcccc agttctacac gccggatgac gggggcactg ytcacctgtc 300
tgctgctgca raggacggca gtgctgtgtc cgccaccagc accatcaacc tctactttgg 360
ctccaaggte cgctccccgg tcagcgggat cctgttcaat aatgaaatgg acgacttcag 420
ctctcccagc atcaccaacg agtttggggg accccctcac ctgccaattt catccagcca 480
gggaagcagc cgctctcgte catgtgcccg acgatcatgg tgggccagga cggccaggte 540
cggatggtgg tgggagctgc tgggggcaca cagatcacca cggccactgc actggccatc 600
atctacaacc tctggttcgg ctatgacgtg aagcggggcg tggaggagcc ccggctgcac 660
aaccagcttc tgcccaacgt cagcacagtg gagagaaaca ttgaccaggc agtgactgca 720
gccctggaga cccggcacca tcacaccagc atcgcgctca cttcatcgc tgtggtgcaa 780
gccatcgtec gcacggctgg tggctggcag ctgcctcgga ctccaggaaa ggcggggagc 840
tgccggctac tgagtgtctc aggaggacaa ggctgacaag caatccaggg acaagatact 900
caccaggacc aggaagggga ctctggggga ccggcttccc ctgtraagca gcagagcagc 960
acaataaatg aggccactgt gccaggctcc aggtgcctcc ctggcytgtc tcccca 1016

```

<210> 41
 <211> 423
 <212> DNA
 <213> Homo sapiens

```

<400> 41
agtgagctgt gattgcaaca ctgcacttca gcgtgggcaa cagagtgaga tcttgtctca 60
aaaaaaagaa ataatactag tttttgtttk tagattttgt atcctgaaac tttactgaat 120
gttttttagt tcgaacagtt tttttgggtg agtccttagg atttctctta cttatgatcg 180
tgtcatctgt aaacagagac agttaacttc ctcccttccr atttagatgc cttttctttc 240
tcttgccata ttgcctaatt acagcatgtt cctattctgt aaatgttcaa tgaactagar 300
aatgattctt gggtagttaa tattgtcaat gttgatgaac tcttttctct cgctgaaagc 360
agctactttg ttggagggtt caattctgcg tggcaatttg cagcatttct agtggtagct 420
ctc 423

```

<210> 42
 <211> 961
 <212> DNA
 <213> Homo sapiens

```

<400> 42
gcctctacca cctcagttac agacaccacc aagggtcaaac agtgtatttg ctgtcaacca 60
agctgtgtca ccaaactttt cacaaggatc tgccataata attgcctctc cagtccagcc 120
tgtactccaa ggaatggtag ggatgatccc agtatctgtg gttggacaga atggaaataa 180
cttttctact cctcctcggc aggttcttca tatgcctttg acagcacctg tatgcaatag 240
aagtatccct caattccccg tccctccaaa atctcagaag gctcaggggc taagaaacaa 300
gccttgtata ggaraacaag taaataattt ggtggattcg tcaggtcatt cagttggatg 360
tcatgcacaa aaaactgaag tttctgacaa aagtattgcc acagatcttg ggaaaaaatc 420
agaagaaacc acagttccct tcccagaaga gagtatagtt ccagctgcta aaccatgcca 480
cagacgtgta ctctgtttcg acagcactac tgctcctgtg gcaaatacgc agggggccaaa 540
ccataagrtg gtgtcccaaa acaaagaaag gaatgcagtc tcttttctta atcttgactc 600
acccaatgtg tcctccacct taaaaccccc ttctaataat gctatcaaaa gagagaaaga 660
gaagcctcct ctgcctaaga ttttatctaa atcggaaagt gccattagcc ggcataccac 720
cataagagaa actcaatcag aaaagaaagt ttcaccaaca gaaattgtgc ttgaatcttt 780
ccataaagca acagctaata aggagaatga attatgcagc gatgtaggaa agacagaaaa 840
atccagaaaa ttcaaaacta tctattgggc agcaaaatgg gggtttgcca agtgagaaat 900
ctatagcttc actgcaagaa atgacccaaa aacaaggcac atcttcaaac aataaaaaatg 960

```

t

961

<210> 43
<211> 545
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (142)
<223> n equals a,t,g, or c

<400> 43
ccaccgcggt gncgaccgct ctagaactag tggntccccc gggctgcagg aattcggcac 60
gagttggagt cctttgctgt tcccaatttg tggaagagtg aagacatcac ccaaatcgtg 120
gccaactatg ggctcatatg tnttactcgg gctggaaatg atgctcagaa gtttatctat 180
gaatcggatg tgctgtggaa acaccggagc aacattcacg tgggtgaatga atggwtcgt 240
aatgacatct catccacaaa aatccggaga gccctcagaa gggggccagag cattcgtctac 300
ttggtaccag atcttgtcca agaatacatt gaaaagcata atttgtacag ctctgagagt 360
gaagacagga atgctggggg catcctggcc cctttgcaga gaaacactgc agaagctaag 420
acataggaat tctacagcat gatatttcag acttcccatt tggggatctg aaacaatctg 480
ggagttaata actgggggaa gaagttgtga tctgttgccct aaactaaagc ttaaaagttt 540
agtaa 545

<210> 44
<211> 377
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (301)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (347)
<223> n equals a,t,g, or c

<220>
<221> misc feature

26

<222> (359)

<223> n equals a,t,g, or c

<400> 44

```

cgatcacccc cgaaccattt catcacgtat tcttcagtgg ctggacgagg agctgccccga 60
cctgtccgtg tctcgcagaa gtagccactt gcaactggggc attccggtgc ccggggatga 120
ttcgcagacc atctatgtat ggctggatgc cctgggtcaac tacctcactg taattggcta 180
cccaaagtct gagttcaaat cttgggtggcc ggccactctc atatcatagg taaggacatt 240
ctcaaattcc atgccatcta ttggcctgcc ttctgtttar gggccggcat gagcccgcca 300
nagcgcactc gtgttccatt cccaatggaa cagtctgtgg gccaaanatg tccaagagnt 360
tgggcaagtg gtggatc                                     377

```

<210> 45

<211> 440

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (387)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (416)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (436)

<223> n equals a,t,g, or c

<400> 45

```

ttggacatcg tggccaactc tatcaagacc acaaatacca cttacaatta attttaaatt 60
attcatctgt acatagtttt ctaaaatgta tataattcaa acagagcatc ttgtaactga 120
agacacacca tatctatgat atcgcattag tccatgtggg gaaaagaaag atcagattgt 180
tactgtgtct gtgtagaaaa ggaagacata agaaactcca ttttgatctg tactaagaaa 240
aattgtttct gctttgagat gttgtttagec tataacttta gcccctaactc tgtgtctcaca 300
gaaacatgcg ctgtaatgga tcaaagttta atggatttag ggctgtgcag gatgtgcctt 360
gttaacaata tgtttggcag gcggtangcc ttgggtagaa gtcacggcc attccnccat 420
tccccggttt aaccnngggg                                     440

```

<210> 46

<211> 525

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (345)

<223> n equals a,t,g, or c

<400> 46

```
gtccggctgg gccgggacaa aagccggatc ccgggaagct accggctgct ggggtgctcc 60
ggattttscg gggttcgtcg ggcctgtgga agaagcgccg cgcaacggac ttcggcagag 120
gtagagcagg tctctctgca gccatgtcgg ccaaggcaat ttcagagcag acgggcaaag 180
aactccttta caagttcatc tgtaccacct cagccatcca gaatcgggtc aagtatgctc 240
gggtcactcc tgacacagac tgggcccgc tgcgtgcagga ccaccctgg ctgctcagcc 300
araacttggg agtcaagcca gaccagcttg atcaaacgtc gtggnaaaac ttggtcttcg 360
ttgggggttca acctcactct ggatggggtc aagtcctggg ttgaagccac ggttggggac 420
aggaagccac agttggcaag gccacaggct tcctcaagaa ctttctgaty gagccyttcg 480
tccccacag tcaggytkag gagttctatg tctgcatcta tgcca 525
```

<210> 47

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (403)

<223> n equals a,t,g, or c

<400> 47

```
ttagaaagar agggggctgg gggccgagac ttctgggtcc ctgtatgttg cagaggggtg 60
catgtcatct ccatggagaa ggctgtgtac gctgtcacgc aatcccttgt aagaggccag 120
gcccttgggg gaggagggag cagctgtggc tcacacagcc ccaggaaacc acctcttctc 180
tcagtgagtc agatagatag agaatcccg tgcagtgaca ggcaagtgc tagccagata 240
gaaagcattt ttgtgtaata actaattttt gtttgcttct ctctctctct tccccgccct 300
ccccatccgg attcccgtgg ctgtgtgcat ctctgscgtg tgtecccatg tctgcccga 360
gtgcgcttct ccgagaaggt cactgtccat tcctgggtgt ctnggcaagg ccgg 414
```

<210> 48

<211> 323

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (274)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (321)

<223> n equals a,t,g, or c

28

<400> 48

```

tcgggtccgg nattegccgg tgccggggac agaaacctcc tgccttctta gttcataacc 60
cccccttaca ttagattcta accctgtggt gatttttaggt tgggatttgg gcgcctgcag 120
atggctccga agccagcctc ttgtgatccg agccacttct ctggcactcg gagcgctggc 180
acccgcggag cccttggttc accggaccgc ctgggaacct ggccggggtc tctggcagcc 240
tcccagggct gaggttcaga ctctgttccg cctnaccag gtccacacct ggatagggct 300
gggagttgag gcttggtttt naa 323

```

<210> 49

<211> 841

<212> DNA

<213> Homo sapiens

<400> 49

```

tcgaccacg cgtccgsaga tttcagcctc acatactaag taaatactga taaataagga 60
aattagaaat ttagtattca taattaaata tgctctaaaa tttcckrtac ttttatttcc 120
tgtttattct taggtagatt ggaaggggga aacagtctgt tctccctaata taaatttttt 180
ctaataacga ttagtagaat atggacattc tatatgacag tgacattaaa agaggctctt 240
tggaagtata tacattatta acataatgtg tacaagtcct tttgaaatga caactttaat 300
gggttttcagc tcttttatct agagcttgag ataattcaag ctgagttttt cagggcatat 360
cacaacggca aagtgttcag cagtgggata tcaatgctta ttacattttt cctactgcta 420
tttatataaa atgttattcc attcagagga tgccttttat cccacatta aagcacagat 480
cattaagcaa taaaaaccaa attgtctgtc attcaaatta taactgcagt tatttttgca 540
tggtaaagat gaggtgctaa ttttgtgtga gatgaacttt gtaaactact ttgggaaatg 600
ttcttttgaa gtaaggtttt ttctccttta gtcttatgct tccacttttg tctcagattc 660
acaatccatt aaaamawggg gaaaaaagaa aargtaaaat tgagagactt ttgttagagg 720
agctatttgg aatgaaccaa cattycasat ttcccaaaat gtaagttagg aagtctccat 780
kgycyckgcc attacaaaaa tacactgkta ctatcttaat ctcaagagtg tcattacagt 840
g 841

```

<210> 50

<211> 534

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (423)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (430)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (524)

<223> n equals a,t,g, or c

<400> 50

29

```

aggaaattta gaaaatgatg aattccttgtc cattttttgta atcaagattt taggaaaaac 60
agaagtacat ctatctttat gaaattttgg gcaggttttt gtgtatcaat attttgtact 120
tttaggggaat attttatttt ttagttattt gtgtcaaatt ataattataa aaggtagagc 180
agaaaatata ccatgttttt atataggttc acacctgtac ttaggaggga ccctgtccat 240
ctatatactt tttgtataaa attttaaaat gttaaagatc cacaaggtct taataaaatg 300
attctatagc tagaaaaacc attaccttcc cagtggcttg cactaaaata tacctgggaa 360
aaggaacctt gaaagactgg taactaatgc ctggaaatgt tctatattga atgtaccatg 420
ccnctgggtn gggaaaaaatg tactaataat gggaaatggga aataaaccca gaaatccgaa 480
gttaattcca gcctaaaaaa aaaaaaaaaa aaaagggggg gccncccta gggg 534

```

<210> 51

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (222)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (250)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (265)

<223> n equals a,t,g, or c

<400> 51

```

ggcacaggaa aaagcacttt cttaagccta cagtatcaga tcaatgggga aaacaacaga 60
aaactaagag gagaattttc ccgttaattt tcttgcagaa aagtataagt ctaattgccc 120
attgccataa attttgtctt gtactcagag aagcaacatg cactggctca ttttatgtgc 180
aaagaaaaaga ttccaccatt aaaaaaatta acttggctag gnatgggtgc tcacactggg 240
gaatcccagn cactttgggt ggctnaaggc agatagactg cttgaaacct aggaattcaa 300
gaccagcctg ggacaac 317

```

<210> 52

<211> 1789

<212> DNA

<213> Homo sapiens

<400> 52

```

ggcacgagga aacggacaac aatgttggtg ccaaaactgg atcaggctac cataatcttt 60
tttcttacat tccacttttc tatcttttcc aaatattcca cagtgatcat gtattaattt 120
ttctcttatt ttgatgttgc aaatatattt tttattatgg aaaacggcaa gctacatatg 180
gggaaaaaaga aaaattgaaa ttatgcaatg gcctaccact caagagataa ttattaagat 240
tgtgggtgtac ttttttctat atactttttt ttaaaggaaa ggatcttact ctgtcgacca 300
gcccctcacc tcctttgact agctgggatg acagcacatg ccaccatata caagtatttt 360
tgtatttttt gtagagaagg ggtttcatta tgttcaaact cctcagctgg cctgcttgat 420

```

30

```

ccgatgcttg ttagccttga catttacaat gaacacaagt gtgttgccat cttctgtctt 480
cttcacagac aacttagtag tcaggggaac ttgatgatgg ccaagtgggc aagctcctca 540
gggctgtctt ccgtggatac ttgagctgcc ccaggagcca cagcgtctca ggcagctgaa 600
aagtgagtga catgtagggg gtgtgtgtgt gtgtgtgtgt gtgtgtatgt gtgtgtgtgt 660
gtagctgtaa cacctcagcc ttgcctcctt ggccttcaca gcccttgctt tagctttggc 720
tttgagagag gcagaggctc cctcttttgc cctcactgtt atcttggtga aaagccagtt 780
tggcagtttc tttttttaa aaaatgcaag tatcataatt cagcaatcac atttgggggc 840
aatttatccc agagaaaggg aaatttatgt tcacataaaa acctgaatta acttcaaggg 900
aatgttattt aacaaacagg ttttctcact taactgatta tattcttgat ggatacacia 960
attaaatctt aatacaatat ctccagtggg tcttccaaag ttgtatctgt tttcatgggc 1020
cagaatgagg gaaagtcatt ctggccattc tcttttgcag agaaggatcat tctcttttct 1080
atatgaggag catctctcaa ctgcaagggt cagctcaaat atctgtctat gtatagatac 1140
gactttcaaa gtctagatag gaatggcttg aacataccat ccacatttta tggaaaatcg 1200
cttggtttct ttttccccctg tcttaatctg tttgtgctgt aaacaaaaca aaataccaga 1260
gactggataa ttataaaaca gcaggagttt atttctcaca gtttcagagg ctgggaagtc 1320
caagatcaag gtgcccgcag gcttgggtgtc tagggaagga tcattcctta tagatggtac 1380
catctagggt tcttcacatg gtaaagggaa ggaagggcaa acagggacct agttgggtccc 1440
cgccagacct ttcataagggt cactagtccc actcatggag gctctacccc catgacttga 1500
ttttttccta aaggccccac ctcttgacac tgttgcatg aagattaaat ttcaacatga 1560
attttgaggg gaatgcaaac attcaaaca cagcactccc tcactatag atttctacaa 1620
ctttcagatt attgcagcaa gtggttccat ctgtaaata cttggctagc ttatgtgtgt 1680
tgtctctctt ccataacaca tcaacccaag atttccaaca aaagaataat aacttaaaac 1740
aacaacaaaa aaactcactc acacaaagta tgtgtataag caggttgta 1789

```

<210> 53
 <211> 654
 <212> DNA
 <213> Homo sapiens

```

<400> 53
aatcggcac aggcattgggt gtccctctgt actcagaatg ggttcagsec aagtcggtra 60
aratggatgt tggcaaaata ggaggatacc ctcatcttgc gaatggggga cctgctctga 120
gcctgcccag kggccaggcc tgctccaggt taaactggac ggaaggccca ggtctcagtt 180
tctttcaacc aggagaggcc gctgcctaga gcccctcccc accttttccct ggatgggtga 240
ggcaagccag gagagcaagc agtgttgtcc tcacgggagg aggactgagc gactgggaaa 300
actcggctct acatctcacc cagaacggct ttagaaaca ccacagctgg agagtcctgg 360
ctgagccttg ggagtttcag ctctttggcg ggggtgccag gtgccatgcg atcagcgaag 420
cctgcgagtt ggcaggactc tgaggtttcc tgcagaccat gccatgagat tgaagggtgcg 480
gggaaataaa gaaaaatcac catttaggag actccattct tccctacaa ccagctgtg 540
gtcccagaga tcaggggggtg ttgccagggtg tggctgggga agggctctggg ttcacaaact 600
caccggcact ctttagtccc cgtataacat ggtggttaag gataaagatc ttga 654

```

<210> 54
 <211> 334
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (154)
 <223> n equals a,t,g, or c

31

<400> 54

```

ggcacgtagg ggatgcccac cgccagtcaa aggggttgggg gtggtctctg caccttaagt 60
actaacctgc cgcccacgcg cctcctgacc acagcacccc gtcggctttc taattctgtg 120
agctgccctc gtgggcgtgg cctccctgtg gagntcccca tgtgcctccc cttggtccag 180
cctgcagcta ggaagtgggt cacagcgacg gggctgggct gggccaggcc aggctccggg 240
agatgtggaa ttggcgaaac aactgcccc aatgtatcct ccgcctaggr ctccaagagg 300
tgggaattgg ggcactacgg ccgggtaagg cagt 334

```

<210> 55

<211> 474

<212> DNA

<213> Homo sapiens

<400> 55

```

tgcaaacatg atggatgggg aaagcatagt aactgtactc accaacaaga tgctggagtg 60
acctgctcag atggatccaa tttggaaatg aggctgacgc gtggagggaa tatgtgttct 120
ggaagaatag agatcaaatt ccaaggacgg tggggaacag tgtgtgatga taacttcaac 180
atagatcatg catctgtcat ttgtagacaa cttgaatgtg gaagtgtctg cagtttctct 240
ggttcatcta attttggara argctctgga ccaatctggg ttgatgatct tatatgcaac 300
ggaaatgagt cagctctctg gaactgcaaa catcaaggat ggggaaagca taactgtgat 360
catgctgarg atgctggakt gatttgcctc aagggascag atctgacctg aractggtaa 420
tggagtcact gaatgttcag gaagattaga agtgagattc caaggagaat gggg 474

```

<210> 56

<211> 367

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (250)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<400> 56

```

ccggcctcaa gcaatcctcc cactggcctc acaatgttgg gattacaggt ataagccact 60
gcacacggcc ttactatgct atcaattcca tatatggaaa ggtgttttcc ctttcagagc 120
tctttaaagc tctgcagaag atttacatgt gtttatagag ctaagagaaa tcagggcctg 180
gaaattgagt gtgtaataaa aattaaactc ttcattgtat ataactatgc ataacttcta 240
tcttcattcn cnggaagtgt cctagagcac catcacagct aggaagcttc catcatggat 300
taccttattt cccaaagcaa gtactccaat aattgtctca agagaggaag gacaactggg 360
taccagc 367

```

<210> 57

<211> 564

<212> DNA

32

<213> Homo sapiens

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<400> 57

```

caaccccccta cagatatcaa gggaccacta tacacattag gatgatctat attgaaatct 60
acatggaaca gagtgggact tctaattgta tgacttcaag attttgcttt gtttaaatta 120
ataactgttt tcagaattaa gtgcttaaaa acaaatttga ttgaaaagtt caagacaaga 180
attttgctct ctatggctgt tccatataaa tttgatgggt gattctgaat gtaaattgact 240
gaagaattaa aaaataagaa attccttttt aaaaggcatg cctcttgac tgtgaacaag 300
acagtagtcc cttaaaccat gaatatgtca gtgttctatg gattacgaaa ttagtaatgt 360
tgcttagccc aaacgtgttt tttaaaaagt atagttttgt acatctcyaa gttatcaaac 420
ttcaaaattg agaacaaatt taaaagtcca tatatgcaac tctagtaagc acttaatagg 480
ttacatagca ctggttaaga acaattaatt ttgtttctat attattacta attattatta 540
cnaatcaaaa aacactgtga taag                                     564

```

<210> 58

<211> 444

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<400> 58

```

ggcacgagggg aaaaccataa ctgcctctta atttaacata gaataataca tagttctgta 60
tttttttttaa agtgagctta atgggtaagt attttttata tgcttttagct atagctaaag 120
aaaactgata cttaacaaag ttgaatagta ttattcactg gtgctcctaa aatattgttt 180
ttcagtgtaa aatatgcata tcttctatat ttaatatgaa agtcttgaaa tgtatcagac 240
agaagggkat ttcagtttgc aaataatgag caatgtagca attttaacac atttcataaa 300
tatatatattt gtcattggtg gagagcacca tttgttggtt tgaatatact tttaaaggnaa 360
gaggtacaag ggacataaat gntgagatta cctacaggat ggaaatagca gtacagttcc 420
attggtagat attttgaaat gttt                                     444

```

<210> 59

<211> 347

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

33

<222> (327)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (328)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (340)
 <223> n equals a,t,g, or c

<400> 59
 ttgagctcta aatgcaaaac tcttttatac tgaaaaaaca cttaaagyag ttttgtgtgg 60
 catcacagtg atttgtcatg aaaagccata tatggggggac atgctaaaat ggcttctgaa 120
 tgaaatacga cagcagagaa agatgccact gaaatgctga aattatcttt gctgagcagc 180
 ttttgaatgc taagggttcc agtatgtgac ccaaagaagg agttgtctca actccttggt 240
 acagggttca ttcaaaccac caagctgtga gagtgtgttt atttttaatt ttttaaaagg 300
 tattttaattt ccaaccacac ttcttanntt tttggaaaan gacaatt 347

<210> 60
 <211> 322
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (245)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (321)
 <223> n equals a,t,g, or c

<400> 60
 agctggggcc aaaaatagac cagaattatc tgctacttga atgtttggca aaactctcct 60
 agaaaaactga gtctgatgtt tgatttgtgt aaagacttct ttaacttttc taactcaatt 120
 ttactaagt tataggacta ctcagatctt gtttcttttt tgctcaattt tgggtcaattt 180
 tgtttttgtc tatgtcacct aagtttycaa atgtattggc atgaatattt ycataatatt 240
 ccctnattat cttttacatt tctgggggtat cttagcggtg tttccctttt tatccctaaa 300
 atgttttatcc atgcttttctt nt 322

<210> 61
 <211> 834
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature

<222> (793)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (810)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (834)

<223> n equals a,t,g, or c

<400> 61

```

gatatgatgc ccctccttca taattatgta acagttgata cagacacact tctgtctgac 60
accaagtatc ttgaaatgat atacagtatg tgcaaaaagg ttcttacagg agttgcagga 120
gaagatgcag agtgtcatgc agcaaaattg ttagagggtca tcattctgca gtgcaaaggg 180
cgtggcattg accagtgcac tcccttattc gtggaagcag ccttagaaaag actgacaaga 240
gaggttaaga caagtgaact tcgaactatg tgtctgcaag ttgcaattgc agctttgtat 300
tataatccac acctactact cmatacctta gaaaatcttc gcttccctaa taatgttgaa 360
ccagttacma atcattttat tacacagtgg cttaatgatg ttggactggt tcttggggct 420
tcatgacaga aagatgtgtg ttctcggact ctgtgctctt attgatatgg aacagatacc 480
ccaagtttta aatcagggtt cyggacagat tttgcgggcy tttatccttt tatttaacgg 540
attgaaaaga gcatatgcct gccatgcaga acatgagaat gacagtgatg atgatgatga 600
agctgaagat gatgatgaaa ccgaggaact ggggagtgat gaaagatgat attgatgaaa 660
gatgggcaag aatattttgga gattctggct aagcaggctg gttgaaagat gggagattga 720
tgaaagattg ggaagaaaaga tgatgctgaa agaaactgct ctggaaaggc tattcccaca 780
atcattgatg atnaaaaaat aaccctgctn gatnaatttc caaatatttt aaan 834

```

<210> 62

<211> 1796

<212> DNA

<213> Homo sapiens

<400> 62

```

aggggcaaac ctaacctggg atctgacggg atgcgttttg ccagctcaga tctcctctgc 60
tactggaaac ttgcattatt tacagccatt aggagctccc tggttccat tccactcatg 120
actagcttta cctcttttgac cccactgtat tattgtctag ccagttcag ctgaatcttt 180
caacacaaaa tatacagggg accccttcct ggggaacttc ctttgttatt gaggtcttcg 240
ctgatggctt ctccattttg atactcagtc tcagtcacag taggattacg gaatcttttg 300
ccagagtatc aatctacatg ggtgctacac attactgaaa aaaattagga acatgggtgct 360
agttaattca agtcttcacg taaaacttct tctatcatag tggacattaa aaaaaatctc 420
tctgcaaagt gcattgaccc tacctctagt agatgaatgt tgaacaagta gcctatctag 480
gaagcaagtg actagcatcc atgggcatcc cacaggttgt agtccagccc cgatcttggg 540
ggttgggatt gatgttgctg ccaagtccct ccgtttcatg ttcaggctct gcctatgttc 600
ctggtgtctg gtacctgatt tttcaggatg ctgacattta cttcttgccc acaacaccat 660

```


35

```

ataccctaag tcttgccaac atctttgaat gtcttctgct ggtctgtctc tcctccgttg 720
ttcttttact atgtcccaag tgcattgcttt gtccagtcac tgcctaagtc tcaggatamt 780
gatttttagct ttttactagg tcctgacatt cccgtagttt cctcttacct ttctggacat 840
gccagacaaa ctctgacctt aggttctgtg aaaactggta cctgcagaat tcctcagtgt 900
ttgtttatat gaaagtccat tgtgcctctt gattgtgggt gagttgagga aaagaggtaa 960
agcagtgggc agaggttgca acatttattt gggttatagga cacctttgct actggagcat 1020
cttgtagggt aatgtagttc agaacatgca tggagaaatg ctgccataga gtagtagtga 1080
catttgggac ttgaaaaaaaa tcttaagagc aggtataatt ccctcaacaa cagaagaaca 1140
tcagtgcctt agaatgtttg attttgaact ttcttgatgt tttctctgcc gttctgtagt 1200
gttattctaa ttaaaatctt tcctctaaac tctgctcttt tttttccaat tgagcaaatt 1260
cggcatttat tgaggcccta ctacatgtca tatgctgttc tatttgctgg aaacacaaat 1320
gtgaatatgg taggcctgcc cttaaacaaat gaattacagt gtaaaatgaa ctttttataa 1380
agctggctct atatcaatct aattattttt tttttcttca tttcaggcct aagacagctt 1440
tattttcttt ccactccaaa taatgaagaa tccccctagg gcaaagaagg aatttctgag 1500
catgttataa aaaaatagaa aataggataa gttgcgtgaa gatttaatat ttctatacat 1560
caaacctac cataaacaaa attaaaaggc aaatagtaaa cttggaagaa catttgtaac 1620
ataaaagaca aaagttaaat atcataataa aataagcaca tagtagcttt tagtaaatca 1680
ttgctgaatg aatgaataca tatatgaatt caaagcaatg aaaaaatcac ccaggaaaa 1740
gatgtaaaaa tttgacatag gacaagtcac caaaaaaaaa aaaaaaaaaa ctcgta 1796

```

<210> 63
 <211> 1376
 <212> DNA
 <213> Homo sapiens

```

<400> 63
ggcacgagtt ttggactagg tgcacagtt attaaaacaa cttttaaccc tcccccttca 60
cacacatata tatcagggttg ttttctagtt aaaaacccaa gtagctcaga ttctacttta 120
atgtcagtcg agatttgcac tgaatcatgc cattatgttt tttctcattt ttatgctgtt 180
gggtcttagt ttttaaattg atataaagaa ctacagcaatg gttttatttt ctactcatat 240
ttagggttta ggaaacacta ccactagtta tcatttaatc aacttcaatg gtctactgaa 300
acaaaaatgg taacttttca ttagtggatt atttagagtt atagtagttg tttccagaaa 360
acacttcctc acaattgtac ttcccaatca aatcatgtga tcatacagtt attcccatga 420
aaggcagaat gtttgtttca aaattaatct agttttctgt acattttaat ttgagaagggt 480
gacaactggc tcttttccag tcttccttca tgtcagtttt ctgatagacc actattggca 540
aacagtatct gtcaactacc aaatgtgtaa aattttctgt atttcacttt gtcttatttt 600
taaatagtga actaaaactt ttggcagatc agcaacattt gctgagcctg ttttttaagc 660
taatgtgtat tcttactaat gttcctatca agaattgatt tgaatatata gctgtctatt 720
tctaattgtt acattcatat tttgagggtt tatcttattt taatagagaa cagacttctc 780
aaaaaatctt cagaagcagc ttattattga aatatcgaaa tattgaaata aaccgggtgg 840
ggttagatta ctcatctgtc caccaagtgg gacatttgca tggactgggg gcttaaagga 900
cttagaagag acctgtaagt aaatcctgaa aatgagccaa tccccacttg aatggttact 960
ggagtaaacc cacctttacc accccaatta cagcacccga ggccgataaa ccaacttggc 1020
tctggttcat ttttcttttc ttcatattgt atgctcagat tcaaaatgtg tgttctacac 1080
tggttacaggc ttctcttttg tttgattaaa gattttagtc ctacttttgt atggacacat 1140
tagaatattc agagaccaa atagaagaat ttgctgttag atatttttca gaagtcagca 1200
gatttgtggc aaatcattta tttgcctttt taaaaattca ttttaagcag tcagagagta 1260
gactactcag aaaattattt cacgtaattg tctaagagggt caatattttt taatgcatat 1320
tgaatcaaat aaagtgtctt aaagaaatta ttctccaaat aaatttttaa aaaaaa 1376

```

<210> 64

36

<211> 574
 <212> DNA
 <213> Homo sapiens

<400> 64
 ggcacgagct gaaaggtggg ggaagggaac gtagacctag agaggggaat tcttacagaa 60
 atcctctttt tttggtccct tctatttttc agtctccggc agcctcttgg tcatgaaagc 120
 cctcagattg tcggcttccg cctctttctg ccttctgctg atcaacgggt taggggcagc 180
 accccctggg cgccctgagg cgcagctcct cctctcagct ctgagcataa agagccggta 240
 gccggggacg cagtggcccg gccaaaggat ggcagcgccc cagaggtccg aggcgctcgg 300
 aattccgagc cgcaggacga gggagagctt ttccaggggc tggatccccg ggcgctggcc 360
 gcggtgctgc tgcaggcact cgaccgtccc gcctcacccc cggcaccaag cggctccagc 420
 caggggcccg aggaagaagc agctgaagct ctgctgaccg agaccgtgcg cagccagacc 480
 cacagcctcc cggcgccgga gagcccgag cccgctccg cctcgcctc agactccgga 540
 gaatgggccc gaggcgagcg atccctccga ggag 574

<210> 65
 <211> 603
 <212> DNA
 <213> Homo sapiens

<400> 65
 cccacgcgtc cggctggact gttttgatct cttttaattg ttctgacaga tagttgggga 60
 tgagagccga ataaggtttg cctgaaataa ctgacactat ataatttctg ctttggcaaa 120
 tactaagttc taacttgtca ttccctggtag aacaagcttt atttttcgag cctagcaatg 180
 atctagaagc agatgttate tcagtgcctt ttgcaatttg ttgtgtgggt tttttttttt 240
 ttaaagccac acaataattt tggaaaacaa tgtatgggta gaacatgtgt ctgttaattg 300
 cacacaaaac cactttttaat gggtacagag ttaaatttga aggaataagt tcataatact 360
 gaagctagaa ccaagcagaa tctgtttttt tctgaggagt atcggtagca taaatgtgat 420
 tataaacata gtacacttga tatatggagg cagtgcagc tattttttaca aaattttaa 480
 ctgcaaatgg attcaacatg tttatgggtt attaaaattg tctgatttct taggttcttt 540
 atagtacacg tgttgaaaat aaatgattaa gaattgtttc aagaaaaaaaa aaaaaaaaaa 600
 aaa 603

<210> 66
 <211> 1772
 <212> DNA
 <213> Homo sapiens

<400> 66
 tcgaccacg cgtccgggag gatccccagc cgggtcccaa gcctgtgect gagectgagc 60
 ctgagcctga gccgagccgg gageccggtcg cgggggctcc gggctgtggg accgctgggc 120
 cccagcgat ggcgaccctg tggggaggcc ttcttcggct tggctccttg ctcagcctgt 180
 cgtgcctggc gctttccgtg ctgctgctgg cgcactgtca gacgccgcca agaatttcga 240
 ggatgtcaga tgtaaattgta tctgccctcc ctataaagaa aaattctggg catattttata 300
 ataagaacat atctcagaaa gatttgtgatt gccttcatgt tgtggagccc atgcctgtgc 360
 gggggcctga tgtagaagca tactgtctac gctgtgaatg caaatatgaa gaaagaagct 420
 ctgtcacaa caaggttacc attataatct atctctccat tttgggcctt ctacttctgt 480
 acatgggtata tcttactctg gttgagccca tactgaagag gcgcctcttt ggacatgcac 540
 agttgatata gagtgatgat gatattgggg atcaccagcc ttttgcaaat gcacacgatg 600
 tgctagcccc ctcccgagc cgagccaacg tgctgaacaa ggtagaatat ggcacagcag 660

```

cgctggaagc ttcaagtcca agagcagcga aaagtctgtc tttgaccggc atgttgtcct 720
cagctaattg ggggaattgaa ttcaaggtga ctagaaagaa acaggcagac aactggaaag 780
gaactgactg ggttttgctg ggtttcattt taataccttg ttgatttcac caactgttgc 840
tggaagattc aaaactggaa gkaaaaactt gcttgatttt tttttcttgt taacgtaata 900
atagagacat ttttaaaagc acacagctca aagtcagcca ataagtcttt tcctatttgt 960
gacttttact aataaaaaata aatctgcctg taaaataaat taaaaaatcc tttacctgga 1020
acaagcactc tctttttcac cacatagttt taacttgact ttccaagata attttcaggg 1080
tttttgttgt tgttgttttt tgtttgtttg ttttggtggg agaggggagg gatgcctggg 1140
aagtgggtta caactttttt caagtcactt tactaaacaa acttttgtaa atagacctta 1200
ccttctattt tcgagtttca tttatatatt gcagtgtagc cagcctcatc aaagagctga 1260
cttactcatt tgacttttgc actgactgta ttatctgggt atctgctgtg tctgcacttc 1320
atggtaaacy ggatctaaaa tgcttgggtg cttttcacaa aaagcagatt ttcttcatgt 1380
actgtgatgt ctgatgcaat gcatcctaga acaaaactgg catttgctag ttactctaa 1440
agactaaaca tagtcttggg gtgtgtgtgt ttactcatct tctagtacct ttaaggacaa 1500
atcctaagga cttgggacact tgcaataaag aaattttatt ttaaacccaa gcctccctgg 1560
attgataata tatacacatt tgtcagcatt tccggctgtg gtgagaggca gctgtttgag 1620
ctccaatgtg tgcagctttg aactagggct ggggttgtgg gtgcctcttc tgaaaggtct 1680
aaccattatt ggataactgg ctttttttct tcctcttttg aatgtaacaa taaaaataat 1740
ttttgaaaca tcaaaaaaaaa aaaaaaaaaa aa 1772

```

<210> 67
 <211> 1829
 <212> DNA
 <213> Homo sapiens

```

<400> 67
cggcaccgaga ttggagccta tttagtggat tttatgcagc caaagatggt tcttgttgtt 60
gttgttgttc ttgcttttaa ctaatttgcc tcccaggaga cagttgaaat gtctagagac 120
attttgatta ttatgcctgg caggacgcca ctagtggcat ctagtggatg gagggtaagg 180
gtgctgctaa gcgtcctccc atacacagga cagcaccccc cacaaagaat tatccaaccc 240
caaatgtcag tagtgctgag gctgagaaac cccactctgc tctctaacca aaattagaca 300
cagaaagtgg agacattcta ccaccctgac aacatcaatg gcttttgccc atttaaaaca 360
agaaagagga atatgtatcc aacccaaaac aacatcttaa cattctttct aataggcttt 420
tgcaaaaata gttcatatatt tataactgtc ttgcagcatg ggggtataagt gtaatcattg 480
taaaaatgaa acctaatacat tgtaaaaatg aaacctaatc atggtaaaaa tgaaaagagt 540
gcctcaaaac atctgaagtt cttagcaaaa ggcagcctgt cttcagtggg cacttttgga 600
tggaggcagg actaggggat cagtaggagt gagaacaaaag gtcagaaaaa tgagtacaca 660
gcacatgtat actgattaat ttctttcttt tttccttctt ttgatggagc aagactgtaa 720
cagaagcctg agagttagga agggcttttg caactattac tgtagacaca gtagtttact 780
caattttatg aactcttagt cctgggcttg aattcacgcc tctgctggaa ttgcacagac 840
aaaacgtgct tgcgaggagt aaggtggcaa caaaagaaaa atgcaggcaa aaacacgcct 900
cattttgaaa ccggatctga gcatcctaga gccagagcct ctcccagcca acattgctga 960
gttgagcaga gtgacagact ccacactgga gccagccccg cagctggcca taaggaggag 1020
ccacgagcag gtgctgggaa gacaggcttt tgaacgcaca ctatgctgat gtctctttct 1080
gtgaagtttt ctacatgagt gacgttctca aagtctgcaa cacagtctgc catgagatgc 1140
cttttttctt ctgggaacac aatgctactt tcgtgatttg ctgagtaatg gccccaaaag 1200
atgtactctt catcctaata cctggaacct gtaaacaatg taccttatat ggcaaaagag 1260
acttcggggc ggcacctgtc atcccagata ctcaggaggc tgaggcaaaa gaatcgctca 1320
aacctgggag gcggagggtt cagggagcca agattgtgcc aatgcactcc agcctgagca 1380
acaaagtgag actctgtctc taaaaaaaaa aaaaaaatct ctcagatgtg actcagttaa 1440
ggattttgag atgggggagag tatcttggat tagccaggct tgtgagaact cctgacgtct 1500

```

38

```

gaagcttgac tcccaagttt ccatagcaac aggaaaaaaa aaaatctatc caaatctgaa 1560
gattgcggtt tacagctatc gaacttcaca actaggcctc aattgttccg gttttttatt 1620
ttctttacaa tttcacttag tctgtacttc atcattttga cagcatcttc ctccctcctt 1680
taattaatgg aatcttctga attttccctg aatgttttaa gatcatgaca tatgacttga 1740
tcttctggga gcaggaacaa tgactacttt ttctggtgtg ttaacatgtc ggtgccgaat 1800
tcgatatcaa gcttatcgat accgtcgac                                     1829

```

```

<210> 68
<211> 1688
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (912)
<223> n equals a,t,g, or c

```

```

<400> 68
acccacgcgt ccgctcatgt ggacttatgc cagtctagag gcagaatcag aaggcttggt 60
tgaacatatc gctttccctt tttcctctcc ctccgcccc cccagtacag tccatctttc 120
aatgttgag cctggttgag aaggagagaa aaagggtggc ggaatttcca ggagatcccc 180
aagaatgctg ccttgtctgt ggacaaagat ggaccatgtg cccttcggaa ttagggatag 240
aaacaaatat tgtgtgctct taacgattaa gctgtgttat ggtgggtttt cagggttttta 300
ccttttttct ttaccccttt actctgcaag aatggggaaa gaatgcatac tgcgaaaatg 360
agtcttttaa attctgtctg cctactagtt ttaagtatat ggtatgttgt aaaatttcca 420
atgatgagag acagcacaat aaatgtacct tatctcctta ggctgaaggc cataactaca 480
tagtggagta atttaagaac tctcttgcc tccaacccc aaaagggtgc tttttgatag 540
caactggcta atgaattttt aaaaagagaa gaaaaatact agttttcccc tcttttgga 600
aatagatttt aaatggctaa actactagcc ttaaaactac tagtctataa atcaactacc 660
acttttgtga atctgacagg ccacattttt atatggccct ttacagaatg gagtgtgttg 720
aacaggatac taacgccatg gagttgagct gggcctagcg atggaggag actctaacac 780
aactttccct cagctattat gcaacagatc agggaaaaag atgggatgac agatggggtc 840
agacagaaaag agcttctggg aaacaagctt acatagtctt ttttaaaatg cacaagacct 900
cccagctaag angtcacttg gtttgggctt cattaggact ggagactttg ttggagtctt 960
ttctgggaac ttggagagtg gatgatattc aggctctgaa acattcccag cgctctcccg 1020
agggtgccac tttctcaaga tgaaaactgt gactgaaaaa attaataata aatgtttctg 1080
agctgcctgt gttctccctg tgtgggtgag agaagggact agactcctaa gcctgcctca 1140
gatacaagag ggatcatttg ctccaatttt agagaacttg aaagcaaggc tttggacaaa 1200
attttgagac cctaatactt ttaccttctt ccaaattacc caacatacgg taaacaacat 1260
ttgtgcagaa gtatgtatgt atttagttca ggttgacttg tgctcttata aactgttact 1320
caaatgattt gaacttttat gcgactggga tttttttttt ccaaagctac aagcatggcc 1380
gcctgtggta tcgaggtgtt gcaaacaata tctgtgttgc gcttctctgt ttaacctacc 1440
tcgttttgtt tgtttttgtt tcaactgttc tcacagcagt gttatctcca ggagacatat 1500
agagagctca accggcaatc tcaggtgcat ttaacatttt taaaacgaaa cagtgttga 1560
ccaaattttt cttcttaaaa aattggaagt ggggggaatc caatgacaaa aactaatgtg 1620
gcttgtttct ggagaaaata attactgtaa atggaacaac aacaacaata aaacacacgt 1680
taaacatc                                     1688

```

```

<210> 69
<211> 565
<212> DNA

```

39

<213> Homo sapiens

<400> 69

```
tcattttgtg gacgaatatg atccaacaat agagagaaca aattaaaaga gttaaggact 60
ctgaagatgt acctatgggc ctagtaggaa ataaatgtga ttgaccttct agaacagtag 120
acacaaaaca ggctcaggac ttagcaagaa gttatggaat tccttttatt gaaacatcag 180
caaagacaag acaggggtgt gatgatgcct tctatacatt agttcgagaa attcgaaaac 240
ataaagaaaa gatgagcaaa gayggtaaaa agaagaaaaa gaagtcaaag acaaagtgtg 300
taattatgta aatacaatgt gtactttttt ctttaaggcat actagtacaa gtggtaattt 360
ttgtacatta cactaaatta ttagcatttg ttttagcatt acctaatgtt tttcctgctc 420
catgcagact gttagctttt accttaaatg cttattttta aatgacagtg gaagtttttt 480
tttcctctaa gtgccagtat tcccagagtt ttggtttttg aactagcaat gcctgtggaa 540
aaagaaactg gaatacctaa gattt 565
```

<210> 70

<211> 675

<212> DNA

<213> Homo sapiens

<400> 70

```
ccagcatcag aagttctgat ggatgatgac cttcagaaaa gtgtggatat gatcatggat 60
atgtttttgt ctcagggaat aaaaattgat gcatatccgt gggttggaatg cttcatcaag 120
tcatacaatg tcacaaatgg aacagataat caaatttgct atcagatttt tgacaccaca 180
gttgcgagaag atgtaatcta atattgccat ccaattttagc atacataaaa tgttgccact 240
caccttccct gtttgagctt cttttcctga cctgagtttt gtatcagcaa tgttgatgat 300
gttagcatgg gtatgggatt agaaaatgtc cttaccttaa atctcttggc ttttactggg 360
tgcaaggtaa ataatggcta tggattttgt tttgctttct gttttgcttt tgtacaaaga 420
gacctgctta aacaagtact gctgagataa gtgtctgate aagctacagt gtactttaag 480
tagaaatggc aaagtttgct tgttgggggtg ctgatactga tgatttttagg ataaattcat 540
ttcttttaac ttgtaataca tggtttttatt gcttgtttct cyccaggata gtagagattt 600
ctctattttc cctcaamcta ataaaagtgg tcagattttat aatgttaaaa aaaaaaaaaa 660
aaaaaaaaaa aaaaa 675
```

<210> 71

<211> 270

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (247)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (260)

<223> n equals a,t,g, or c

<400> 71

```
ctgagatgcc acaagaagca gcacagtgat cagagtgaga acaagaactc agacttgggtc 60
accttcccac cggaaagcgg tgcctcggga cagctcagca ccttgggtctc cgtggggcag 120
```

40

```

ctcgaggctc ccctagagcc cagccaagac ctctagctca gccgaagagg gtgggtcagct 180
gtcggaaactt ctgaccagtg ctgttgccca gccctccaga ggtgaggcca ctgagagaca 240
ggctttnggc accacttctn gggctggccg                               270

```

```

<210> 72
<211> 538
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (101)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (302)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (449)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (459)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

```

```

<400> 72
tatctcttgg cagcaggggt tgcaactgag aaacatgcaa ggtgggggat aattggatct 60
tgtgggtcag cctaccaaag tgctgggatt acaggcgtga ncaccatgct cggccagtca 120
gtatcatttt ttaaaaatgt agaacctggg ttgatgactc taattaaatt gtctgccaat 180
tactgaagag ctactacata ctagwttctg ggcttttagtt ctaaagccca cagcaacctc 240
atgaataaat attattagcc cactgtata gatgagataa cagactagga gggagaagtt 300
anggaaactt gcttaatgcc tcctgttttag aaaatagctg aactggaatt cagccctgtc 360
ttccatttca cctgcctgt gtctcacgca cagaacaccc ggggatccgc tggttcccaa 420
agcactgatg agaaccctaa tttgtcaana ttctgggnt ccagtaaattg gtgggtccaga 480
atggtgggtg atctgatttc atattatctg ccaggtgaaa ngtttctgcc tggcaaaa 538

```

```

<210> 73
<211> 1071
<212> DNA
<213> Homo sapiens

```

```

<220>

```

41

<221> misc feature
 <222> (1010)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1048)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1062)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1066)
 <223> n equals a,t,g, or c

<400> 73
 ggcaggaggc tgccggggcg cgggctgctg cgggagaagg ggctccgagg agtccgccgc 60
 ggctcgctct gtccggcgcg cgggattggg gcgcgagggc catgggcgcg ctctcctaag 120
 gcggagggtcg cgggcgggag gggaggaggc ccgagagagg ctgctgcgaa ggccgcgggc 180
 ccgtgactgg gcgcgagggc gccggcgggc gcggcggcac cagcaccacc atgtcgcgct 240
 cagtgtgca gccagtcag cagaagctgg cggagaagct caccatcctc aacgaccggg 300
 gcgtcggcct gtccaccgc ctctacaaca tcaagaaggc atgtggagac cccaaggcaa 360
 aaccatccta tcttatcgac aaaaacctgg aatctgctgt gaaattcata gtcagaaaaat 420
 tccctgctgt agaaacccgc aacaacaatc aacagcttgc acaactacag aaagaaaaat 480
 cagagattct gaaaaatctg gcattatatt acttcacatt tgtagatgtt atggaattta 540
 aggaccatgt ttgtgaattg ctgaatacta ttgacgtttg ccaagtcttc tttgatatta 600
 ctgtaaactt tgatttaaca aagaactact tagatttaat tataacctat acaacactaa 660
 tgatactgct gtctcgaatt gaagaaagga aggcaatcat tggattatac aactatgccc 720
 atgaaatgac tcatggagca agtgacagag aatacccacg ccttggccag atgattgtgg 780
 attatgaaaa cccctttaaag aagatgatgg aagaatttgt accccatagc aagtctcttt 840
 cagatgcact aatttctctt caaatgggtat atcctcgaag gaatctttca gctgaccagt 900
 ggagaaaatgc ccagttattg agcctcatca gtgcacctag tacaatgctt aatccagcac 960
 agtccgacac tatgccttgt gaatacctct ctttgggatg caatgggaan attggattat 1020
 ctttggcctt atttgtgcc a tggggatnct taaatacttg angctncagt a 1071

<210> 74
 <211> 640
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (93)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature

<222> (96)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (619)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (624)
 <223> n equals a,t,g, or c

<400> 74
 gttgcagtga gccgagatca caccactgca ctccagcccc ggtgacagag caagactccg 60
 tcataaatga ataaataaat aaataaataa tangtnacga tccattgtgg ctctctggaa 120
 acatccatgt tcacagctgg ggtctggtca gtctgcatag tggagcacac tgctaggatg 180
 catccttagc aagtgaaaaa agtgaggctc agaactgttt gtagagtata gccttttatc 240
 taaggaaggc agatgaagac tggcttatga taaaggtgct aacccccaga ctagtaaaaa 300
 tgggggtccc tgtggagtag ggaaggggca gtgttataag ttggatttct ggccatatct 360
 gctatagtac tgatcatgga actctagggg aggaaagatg ttttccttct acccatctta 420
 tgttcattgg ctggggctcc tggaacagaa gacagatttc caaagagaaa ggcacacmaa 480
 tttatgtaat ataagtttgc catgacmtgg gagcctttat aaggaatgac cccaaggaaw 540
 tggttaaacc tgagtggttt tgtgtaaggt tttaatgagc aatgaaaagc tatgggggacc 600
 tatgatagga ggatgtaanc taanccaatg acctggggga 640

<210> 75
 <211> 507
 <212> DNA
 <213> Homo sapiens

<400> 75
 ggagcttcaa catatgaatt ttcaggggta tcattcagtc caaagtactt aakatgatct 60
 ttttccggtt ccacatagac aatcacataa tctgtaaata atgactctta cttttccact 120
 ttagtcgtta ggttatacct atatatatat wwwmwtgctt tactggacta atttcaacct 180
 ccagcacacc accaatgaat agcagtaata ccagcataat tgtctgcagt tctgctgaga 240
 tacgtgctct attttattgg cttggctgta ggtttttatt ttattttttg aagaggctaa 300
 tctcttacag gaaagggttc tttttatata cagttttttac atgatgaatg atttccagct 360
 atttcataat tcatgaggct gaattcctct tgaattttatt aaatgcttcc tgtgcatect 420
 ctgtgatgat catgtttatt tactgctaga actcaagtac ctagaactgt tcctggccaa 480
 tgatggtatg taataaatac ttcaatg 507

<210> 76
 <211> 1390
 <212> DNA
 <213> Homo sapiens

<400> 76
 ggcacgaggg agtctgatgg ggagaagaag taccatgcc ctgaatgtgg gagcttcttc 60
 cgctctaagt cctacttgaa caaacacatc cagaaggtgc atgtccgggc tctcgggggc 120
 cccctggggg acctgggccc tgcccttggc tcacctttct ctctcagca gaacatgtct 180


```

ctcctcgagt cctttggggt tcagattggt cagtcggcat ttgcgtcatc tttagtagat 240
cctgagggttg accagcagcc catggggcct gaagggaat gaggcagctg ctgtgtcccc 300
acggaaacaa ccatctgggg actgctggga aatgctgtga atgcggaggg aagtgatgtt 360
tgggttctgt agctgagaga tttttattca tttttaactg ccccccaacc ccaactccaac 420
tccttctcca ccacccattc tcccaatggt ctttagaaat agattttcat ctgatattct 480
gcagaaatat caatgagact tggatatgga caggggcaga aaacactaca taggcctcca 540
aggcaaaacc agtcccagtt tctttaatgg gaagaagctg gaattcctgg tgctcaattc 600
ttagtgaccc caatcctata cccaaatcta tgatattctg ggacctcagt gattttgggtc 660
ccctcccaact tctctagttc gtcatectcc ctccccatat ccttcaaaaag aaccacacta 720
gggtctccac ctacttatac aatgcgggatg cccaactggt ttttaaggaag ccagaagcat 780
cccatggacc atgggggtgag tgtcctccaa gagccccctg agctcagccc tctgcctgga 840
gggctccaga cctttctgag ccctgcttgg aggcgagcat tttcactgct aggacaagct 900
cagctgttga ggacaccccc accccaaatt tcagttctta cgtgatttta accattcaac 960
atgctgttgg gttttaattc tctaattatt attattattg ttattatttt ttaggaccag 1020
ttgtagtgaa ttgctactga aagctatccc aggtgataca gagctctttg taaaccgcag 1080
tcacacatta gggttagtag taaactttgt ttagatgtac cataattaac ttggctagtt 1140
gattgtttga agtctatgga agaaatagtt ttatgcaaaa ttttaaaaaa tgccagtctg 1200
gtcaggggaag taggggggtt caatgctgtt gggaaccagg aaggtgggac agccggcagg 1260
tagggacatt gtgtacctca gttgtgtcac atgtgagcaa gccaggttg accttgtgat 1320
gtgaattgat ctgatcagac tgtattaaaa atgttagtac attaaaaaaa aaaaaaaaaa 1380
aaaaaaaaaa 1390

```

```

<210> 77
<211> 782
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (29)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (738)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (748)
<223> n equals a,t,g, or c

```

```

<400> 77
gggcacgagc tcgtgccgaa ttcggccang aggnacctga gcagtctaac tactccagtt 60
agacctaagg gcacaaatgc agaattcatg accttgtagt tgtggcaggg tctaggaagt 120
cctctctccc caagtagaaa atattctctt gccattcctg aaattccaca ttcatataat 180

```

44

```

ggctgtgcaa tacatgcttc tcaataagaa aattaactgc atgtttactg tgtgctgac 240
acatcagatt tttatgttta aaaaaatctc attatggatt gagtccagcc cagctctaag 300
agaaaaagaa ggcccatatg ggagacttca stctcattat tattgccttt atccagcagt 360
gcttatgaag cccctaccc tgtcccatc cagaaacat aagactcagg cagttcttga 420
ttctggaggc ctgcctggta agataagata gtataatttg gaactgagaa cataccagaa 480
acagcagaac gagggccaga gcagaaaaat gaaaataagt ggagacactt atggatacat 540
tgggtgcaaaa aaagccacgg agcccatact gggcttgata tgactttgag gggacagcag 600
attaatactt aatgagggtt aaacctgacc agtctttcta cagtgcacagg ccacactgca 660
tgaatgggga gaaccaatga atccattgtc ctctgcctat tttcctgtgc acagtcacat 720
tccctcctta agaatctncc ccttccancc tttacattaa ccaagggaca ctgaatcttt 780
ca 782

```

```

<210> 78
<211> 278
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (8)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (27)
<223> n equals a,t,g, or c

```

```

<400> 78
cttctcgnctg cccgtgcaaa ggctccnctg cagaagacat cctytggcag cctgctcttc 60
tgctgctcct tttgctgctg tcccatgtgc tcctgagaat gagaaccctg cctttgcaac 120
aaacatgcc ccggtaaatg caaaaccaca tgctctgtgc cccgagagaa aacctctaac 180
cagcaaggaa aatgtattga tgcattcctc cattttggca cctgraagag agtcttggrg 240
aactgcagga gagggggaaa actggaaaaa aaaaaaag 278

```

```

<210> 79
<211> 828
<212> DNA
<213> Homo sapiens

```

```

<400> 79
gccaatcaat gagcagtata gagaatttct ggaagggaga cacaagaagc tgtagaaag 60
ggcggcttcc aggggaagtcc tagggagtct gggatgaatg agaaacttat cctaacaact 120
tttgggctct ctgaattttt tttagtatct gcaagtattg tacttggtca aatatgttta 180
aggctgcagg ctgtattcta aactccttga aagtgagaac caggtttcac tcatatttcc 240
atcttttcaa cccctagatc agtgacttcc cagggaagta gtacctgcat ttgggggttga 300
cctttgggtt tcccctgtac tgggtctggcc tggcctggct ggaccactgg stggctgggt 360
ggctgtgacc tagccccctc tttctctttg ctctctgtgc aaatgagagt gttggtctga 420
acgatctcta aagcctggaa gaggagcaga tcctctgtgc tcagcccca ctctgtgtca 480
gggaggcctg gcaaccacag tgttctttct cctgtttatt tgttcttga tcttctgaa 540
gccatttcac caccagcctt catcttctct gccagcccca tggagactca agctttttcc 600
agcctatgtc aggggaaggag aaccagagac agcaacctcg ggtgtgaagg gagtgcagctc 660

```

45

```
tgaaccagg actatggcct tctgccactg cctgctttcc tcttgctgct ggggcctagg 720
tcttcttgct gctgcttcc tttccgctaa tcaagagtcc agggaggtgg gaacagcctc 780
aacaaagact ttgaagatga gcggggagga tcgcttgagc ccaggagc 828
```

<210> 80
 <211> 342
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (198)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (215)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (319)
 <223> n equals a,t,g, or c

```
<400> 80
caagttggga agaactgata tcttacggat actgttaaag agaactaaat atggcctgag 60
aaggactccr tattttctata tttgartcct tgtgggtgaa ccaaaaccta gcttaatagg 120
tagacaatat tgaaaaccta acctagaagt atgcacctgt aacaatagct aggtcttggc 180
caatgcctgt ggccatantt cagccattca tacantgctg agtggtcaaa gtctgttcaa 240
ataagggaaa caacgaggtg taaccaatcc agctgttctt taccttactt ccaaattctg 300
tacgtcattt occattttnt gtctataaac cttcttccac ca 342
```

<210> 81
 <211> 537
 <212> DNA
 <213> Homo sapiens

```
<400> 81
ggctttacgg ctgcgagaag acgacagaag ggggggggacc atgttgcttc cgaacatcct 60
gtccaccggg acaccagggg ttggaaaaac cacactaggc aaagaacttg cgtcaaaatc 120
aggactgaaa tacattaatg tgggtgattt agctcgagaa gagcaattgt atgatggcta 180
tgatgaagag tatgactgtc ccattttaga tgaagacaga gtagttgatg agttagataa 240
ccaaatgaga gaaggtggag ttattgttga ttaccatggg tgtgatttct tccctgaacg 300
ctggtttcat atagtttttg tgctgagaac agataccaat gtattgtacg aaagacttga 360
aacaaggggt tataatgaga agaaactaac agacaatatt cagtgtgaga tttttcaagt 420
tctttatgaa gaagccacag catcctacaa ggaagaaatc gtgcatcagc tgcccagtaa 480
taaaccagaa gagctagaaa ataatgtaga tcagatcttg aaatggattg agcagtt 537
```

<210> 82
 <211> 292
 <212> DNA

46

<213> Homo sapiens

<400> 82

```

tggacagaaa attcaatcct ttattttttt ctctgtaaat gcacgggcta tgagatagca 60
acaaaaaatg catagttaat ggtcatagac tttattccaa aacataattg gaaaatagaa 120
wctgagccat tgccaaatgg taaagaaatg aaaagttttc acagtgacta ctgaatatac 180
caagagcttt tggcagtact gctggctttc tgggtgatta attaggtaaa cttggaatat 240
tcccagtaaa agtttgagaa tgcataaaat tataaccattt tgaaaaatat aa 292

```

<210> 83

<211> 352

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (345)

<223> n equals a,t,g, or c

<400> 83

```

ggcacgagtk aaacttgctg ttttgttcct gtgtcttgtc tttgggttggc atttcagtaa 60
gttttttggtg ttctcaaatt ttatctaaat ggataaacta ttaacataga acataaaccc 120
caattctcca tttcattttt ctcttaggca tgaatcatac aaaactcaat atagagcaat 180
gttttgtaatg aattgttcta ttaacaaaga ggagggttcta agatrtaaaag cctcagagga 240
acaggaagga aaaggcgggt ccataaggaa gatgagggtct taaccgggga ngatgctgct 300
tgaggagggc cagagacagt tgtggggagga aatcttttca ccccnttcat gt 352

```

<210> 84

<211> 404

<212> DNA

<213> Homo sapiens

<400> 84

```

ccccccccct tttttttttt tttttttttt tttttttttt tgcgattgct ttaaagaaag 60
ctttattttac tacatacatc ctaagaatgt actgtaaatg gagcaagatc taaataaaag 120
cttttcaaatt ataaagcagc taaagttaac taaaccacta gcaatgtttg aaaacagaac 180
tctaaaacttt ttttttttaca tttatatagt ttgttcttaa cactaaaaaa aaaaaagttc 240
acattttcaag ttataaacttt acctcagtag tgtacatgaa atgggttttga aacaatagga 300
acagataagt ccagataggg rggctcactg atacttaatt ggccatgtca ccaatgtttg 360
tttttaaggg rgtttggtgg ttgccatggt tatcattttt tttt 404

```

<210> 85

<211> 1555

<212> DNA

<213> Homo sapiens

47

<400> 85

```

ggcacaggac agtctcatga ttataactgg tccttcaagt atacagggaa tataataaag 60
ggtgttataa acatgggttc ctacaactat cttggatttg cacggaatac tggatcatgt 120
caagaagcag ccgccaaagt ccttgaggag tatggagctg gagtgtgcag tactcggcag 180
gaaattggaa acctgggaca agcatgaaga actagaggag cttgtagcaa ggttcttagg 240
agtagaagct gctatggcgt atggcatggg atttgcaacg aattcaatga acattcctgc 300
tcttgttggc aaagggttgcc tgattctgag tgatgaactg aaccatgcat cactggttct 360
gggagccaga ctgtcaggag cmaccattag aatcttcaaa cacaacaata tgcaaagcct 420
agagaagcta ttgaaagatg ccattgttta tggtcagcct cggacacgaa ggccctggaa 480
gaaaattctc atccttgttg aaggaatata tagcatggag ggatctattg ttcgtcttcc 540
tgaagtgatt gccctcaaga agaaatacaa ggcatacttg tatctggatg aggtcacag 600
cattggcgcc ctgggccccca caggccgggg tgtggtggag tactttggcc tggatcccg 660
ggatgtggat gttatgatgg gaacgttcac aaagagtttt ggtgcttctg gaggatata 720
tggaggcaag aaggagctga tagactacct gcgaacacat tctcatagtg cagtgtatgc 780
cacgtcattg tcacctcctg tagtggagca gatcatcacc tccatgaagt gcatcatggg 840
gcaggatggc accagccttg gtaaagagtg tgtacaacag ttagctgaaa acaccaggta 900
tttcaggaga cgctgaaaag agatgggctt catcatctat ggaaatgaag actctccagt 960
agtgcctttg atgctctaca tgcttgccaa aattggcgcc tttggacggg agatgctgaa 1020
gcggaacatc ggtgtcgttg tggttggatt tcctgccacc ccaattattg agtccagagc 1080
caggttttgc ctgtcagcag ctcataccaa agaaatactt gatactgctt taaaggagat 1140
agatgaagtt ggggacctat tgcagctgaa gtattcccgat catcggttgg tacctctact 1200
ggacaggccc tttgacgaga cgacgtatga agaaacagaa gactgagcct ttttgggtgt 1260
ccctcagagg aactctccct caccaggagc racctgtggc ctttgtgagc cagttccagg 1320
aaccacactt ctgtggccat ctcacgtgaa agacattgcc tcagctactg aagggtggcca 1380
cctccactct aaatgacatt ttgtaaatag taaaaaactg cttctaatec ttccitttgc 1440
aaatctcacc tttaaaaacg aagggtgactc actttgcttt ttcagtccat taaaaaaca 1500
ttttattttg caaccattct acttgtgaaa ccacgccgag ccctatgcag tctca 1555

```

<210> 86

<211> 455

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (430)

<223> n equals a,t,g, or c

<400> 86

```

ggcacgagcc agagccgact gcaaatcact gaactgagct ggcagctgct taggggtttg 60
catgatcaag gcgattttta taacctagaa gggcctggac tgtagaagca gattccagct 120
gaggccagcag cactgccttg ctgtggtgag cacggcggtc ctgstcttcc ccgccgagct 180
ttctcatcag tgaagtgggg tagtgacagc atgcgagggc acggagctgt cagcaggctc 240
cagagaccat ggccataaag cactgacact gacacggccc cagcaagccc ttkgggaagg 300
gcagccacca cckttgctgc tgytgtcact tactgttgct gttgatttaa ggcaktacat 360
actcaggtyt catagcttgt aaaaamaagg aaaaatgaaa agtcaccatc atcccagcaa 420
aatgtaagggn tcccctgctg cccagattgg aatgt 455

```

<210> 87

<211> 675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (427)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (564)

<223> n equals a,t,g, or c

<400> 87

```
ggcacgaggt cgggctcgga ggaggatcca gagacggagt ctgggccgcc tgtggagcgc 60
tgcgggggtcc tcagtaagtg gacaaactac attcatgggt ggcaggatcg ttgggtagtt 120
ttgaaaaata atgctctgag ttactacaaa tctgaagatg aaacagagta tggctgcaga 180
ggatccatct gtcttagcaa ggctgtcatc acacctcacg attttkatga atgtcgattt 240
gatattagtg taaatgatag tgtttggtat cttcgtgctc aggatccaga tcatagacag 300
caatggatag atgccattga acagcacaag actgaatctg grtatggatc tgaatccagc 360
ttgcgtcgac atggctcaat ggtgtccctg gtgtctggag caagtggkta ctctgaaaca 420
tccaccnctt cattcaagaa aggccacagt ttacgtgaga agttggctga aatggaaaca 480
tttagagaca tcttatgtag acaagttgac acgctacaga agtacttnga tgcctgtgct 540
gatgctgtct ctaaggatga actncaaagg gataaagtgg tagaagatga tgaagatgac 600
tttcctacaa cgcgttctga tggtgacttc ttgcatagca ccaacgggaa taaagaaaag 660
ttatttccac atgtg 675
```

<210> 88

<211> 493

<212> DNA

<213> Homo sapiens

<400> 88

```
gtcgccctag gctgggactc tagtaggtct tcggctcagt tttggctgca gcgcccgcgt 60
agatcgcttc ggccgsgttc tacgcccggc tcaactatga gcckggtgcgc ccaggcggcg 120
gaagtggcgg ccacagtgcc aggtgccggc gtcgggaacg tggggctgcg gccgcccattg 180
gtgccccgtc agcgtccttc ttcccgcgcg cggtgccgaa ccccttcgtg cagcagacgc 240
agatcggttc cgcgaggcgg gtccagattg tccttcttgg gattatcttg cttccaattc 300
gtgtcttatt ggttgcggtta atttattact tgcattggcca ttgctgcatt tcaacagtat 360
gctgtcctga aaagctgacc cacccaataa ctgggttgag gaggtaagaa atattttgtc 420
caaaatatta ggacataata ttaaattaag atatactaaa tcaatataag aagagttcat 480
catagtttag tca 493
```

<210> 89

<211> 416

<212> DNA

<213> Homo sapiens

49

<400> 89

```

gtgggggatgg  tgtcgcatag  cagccgctgc  cgctttggct  tgctcgggac  catttggetg  60
gaccagagt  ccgcgtggaa  ccgcgatagg  gatctgtcag  ggcccgcggc  cgggtccagc  120
ttggtgggtg  cggtagtgag  aggcctccgc  tggttgccag  gcttgggtcta  gaggtggagc  180
acagtgaaag  aattcaagat  gccacctawt  ataaactgga  aagaaataat  gaaagttgac  240
ccagatgacc  tgccccgtca  agaagaactg  gcagataatt  tttgatttcc  ttatccaagg  300
tggaagtaar  tgagctaaaa  agtgaaaagc  aagaaaatgt  gatacacctt  ttcagaatta  360
ctcagtcac  taatgaagat  gaaagctcaa  gaagtggagc  tggctttgga  agaagt      416

```

<210> 90

<211> 1467

<212> DNA

<213> Homo sapiens

<400> 90

```

ggcagaggtt  catcttcac  ttctcagctt  gctccaaatg  gtgcaaaatg  cattccagta  60
cgagaccgtg  gcttcctggt  gcagacaatt  gagtttgctg  aacagcggat  ccctgtatta  120
aatgaatatt  gtgtgggttg  tgatgagcca  catgtgtttc  aaaatggccc  tatgcttagg  180
cctaccgtat  gtgaacggga  gctgtgtgtg  tttgcttttc  aaaccctggg  agtaatgaat  240
gaagctgctg  atgaaatagc  aactggagct  caggtggtag  atctactagt  atccatgtgt  300
aggtctgctg  tggaaatctc  tagaaaagtt  gtgatttttc  agccatatcc  ttctgtggta  360
gatecctaag  atcctcagat  gttggccttc  aaccccagga  aaaagaacta  tgatcgagta  420
atgaaagcac  tggatagcat  aacttctatc  agagaaatga  cacaagcacc  atatctggaa  480
atcaagaagc  aaatggataa  acaggacccc  ctgtctcatc  ccttactgca  atgggttata  540
tcaagtaata  gatcacatat  tgtgaaactg  ccagttaaca  ggcaattgaa  gtttatgcat  600
actccacatc  agttccttct  tctcagcagt  ccaccagcca  aagaatccaa  ttttagagct  660
gctaaaaaac  tctttggaag  cacctttgca  tttcatggct  cacacattga  aaactggcac  720
tccatcctga  ggaatggtct  ggttgttgct  tctaatacac  gattgcagct  ccattggtgca  780
atgtatggaa  gtggaatcta  tcttagtcca  atgtcaagca  tatcatttgg  ttactcaggg  840
atgaacaaga  aacagaaggt  gtcagccaag  gacgagccag  cttcaagcag  taaaagcagc  900
aatacatcac  agtcacagaa  aaaaggacag  caatcccaat  tcctgcaaag  ccgtaactta  960
aatgcatag  ccttatgtga  agtgatcacc  tcatctgacc  tgcacaaaca  tggagagata  1020
tgggttggtc  ccaatactga  ccatgtctgc  acacgattct  ttttcgtcta  tgaagacggc  1080
caagtgggag  atgcaaatat  taatacacia  gaaggaggca  ttcacaaaga  gatcctccga  1140
gtaattggta  atcaaaactgc  tactggttaa  aggaccacca  ttttaattaac  atgattcgaa  1200
agccttcctc  gggttcaaa  ctggattttg  aactgaagaa  gattataaaa  ttattttattg  1260
ttattataaa  caaaattaac  cttttgaata  ctgatttttt  ttcttagtat  ttctaagtat  1320
ctcattaaat  acctaaaatg  gtataagatt  tatcaattgt  agggttatgg  aatctagtaa  1380
taaaatttca  acagcactta  aactgaagtt  tgggttgctc  atacaataaa  cagattgaaa  1440
aaacaaaaaa  aaaaaaaaaa  aaaaaaa      1467

```

<210> 91

<211> 1793

<212> DNA

<213> Homo sapiens

<400> 91

```

ccacgcgtcc  gattttgtcc  tattgttcta  tttttaaata  aatatacaat  cattgttttg  60
cattgaaatg  catatttgta  cattttatct  gataatatta  ttttgggaaa  ttgtaatctg  120
ttgttttggt  tgtttgttaa  gggaagcacg  aagaagaatt  taaaaatgtg  aataaaattg  180

```

50

```

ttaaagatta ccaatagttt cttttctgga cttgaaatag ttacgtttct aaatatgaga 240
aaaataactt tgcctaaaat ttcagtataa tgaccagggtc ttctctccat tttagagaag 300
cagtccaatg tggacagat aagacggcag cgatccagtg aggtcaattc cccacagagg 360
aaagctatgc atacctaact taatggaagg taaactttct ttcaattaat gatgtcctcc 420
ttttctcaag gtgtccaaag acaggagggtg gtctgtaaaa ggttggaatga caactccatt 480
gtccagaaca attactgtga tcctgacagt aagccacctg aaaatcaaag agcctgcaac 540
actgagccct gccacctga gtgggttcatt ggggattgggt tggaatgcag caagacttgt 600
gatgggtggga tgcgcacaag ggcagtgtct tgcacagga agatcggacc ttctgaggag 660
gagacgtctg actacagtgg ttgtttaaca caccggcctg tcgaaaaaga gccctgcaac 720
aaccagtcac gtccaccaca gtgggtgggt ttggactgggt ctgagtgtac tccaaaatgt 780
ggtccaggat tcaagcatcg gattgtttctg tgcaagagca gtgacctttc taagacattc 840
ccagctgcac aatgtccaga ggaaagcaaa cctcctgtcc gcacccgctg cagtttgggc 900
cgctgccctc ctctcgtctg ggtcacagga gactggggcc agtggttctgc tcagtgtggc 960
cttgacagc accttggtct atgctggaag aggagggcag tcagtgtcac ttctgggatg 1020
tgccccagca ctgagaacaa aatgcaggca tccccgggg cagcatcaga gtgcctttct 1080
agagggagcc acgcacagaa tgtaacagga tgaaacagtt tcaagtaagc cttgaattga 1140
aacctgagta ggttaaaaaca attctatttc atagcacatc acaatactgc tgctactctg 1200
tagccacccc catggctaca tgatgcccta ttctaaata ataacaatag cattgtcagt 1260
ggaggtctgg ccaccatggc agaccttcca aaagtagtga gctacataga ctacttaggg 1320
aaccacaggg aaactggtac cctacacctg ggagcagtat ctgccactgg gataaagtc 1380
tactaaaaaa ggaacggtaa atgtacccta atgattaaac cccgtgagat acatatgatt 1440
tccaaatagt ccatttcatt aggaactttt ttgtttgaat gaatgtcaca taggtatcct 1500
cagtaacaca gaacgaaatt acctttgtat tattgtgatt agttgttgct tattatttta 1560
tactcagtaa taatgtggta cactgttaat ttttttgctt ttgtaaatta tattctaatt 1620
tattgccatg tttcctaaca cttgtcctac attcattctc ctgcttgtaa tgaaaatgaa 1680
aaaatcattg taacacttga tggagtgaat ttccacgcca ggcacagaat ttttttgaca 1740
tagataatth agtaaaataa aaattcagct tataataaaa aaaaaaaaaa aaa 1793

```

<210> 92
 <211> 538
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (24)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (53)
 <223> n equals a,t,g, or c

```

<400> 92
gcccaaggat tccggcacga gganttkttg ttggttgggg gccttttggc sgntgacgga 60
gactgccag gtgtgggtcac catgttctct tccgcggtct tctttgccaa gagcaagtca 120
aaaaacattc tggtgagaat ggtgagcgaa gctgggacag gtttctgctt caacaccaag 180
agaaaccgac tgcgggaaaa actgactctt ttgcattatg atccagttgt gaaacaaaga 240
gtcctcttctg tggaaaagaa aaaaatacgc tcccttttaa cgggtggattg aaaatgactt 300
tgatttataa agagaagact gagggcgggg atactgattc agaaatcctg tagcgtgtaa 360
taaaagaaga ggaaatggca tggaatcact gcctcctgtg atttgaaggc cattgtgaag 420

```


51

gaaaacaatg cagtgaaaga aagttcttca tattaggaca gatatcattg catcacattt 480
 atttatcttt ctgggtattt ttatagccct taataaaaaa tattaaaatw gwaaaaaa 538

<210> 93
 <211> 483
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (444)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (483)
 <223> n equals a,t,g, or c

<400> 93
 gggaatctat cataactagt ctagagattt ctcaccaagg gaaattttcc ttatctaaaa 60
 gaggaacttc aggtctcaac cctgccagtc acaccaatt aatgtccttc acaaaaataa 120
 acagcatatg ttccctttca atttgagttc agtgagctca cagcaaaatt taccttttaa 180
 ttttcttcag caaatccaag acgaatatac aaaggatgag attagataaa gatttcagtt 240
 tcccgatgc caccgctggc cgccaatttt ccaaaaaagc ctggctcctc ttttctgtt 300
 cctccatcca agcccccaaa gatctctaac cagaawtaaa caggaagact cagtgattta 360
 caaaagacat tttagtttta cacgtacaga aaattctacc cagcattaca gaaattctta 420
 gacttcttaa aattcccggg tttnccttgg tatttaacat ttggataagg gagccatggg 480
 ttn 483

<210> 94
 <211> 719
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (619)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (633)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature

<222> (643)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (646)

<223> n equals a,t,g, or c

<400> 94

```

ngggaattgc tgagatgaca gtgtcccaca cagcttcaaa taaaatccat ggaaagatgt 60
tgcatttgtg gaataagtgc ttacttgaaa agcatgttct tcttttattt tcttactgtt 120
aagaattttt atttgtagga tgtttgtttt aatttaattt ttttaaggga tgggggcat 180
catgtggaaa ccagaaaatg gggaaagtgt gaactatcca gacaaagatt cattttgtgt 240
ctatatattt ttttaatttg cctcatttca aatgtattaa acagtcccat acctggattg 300
ggtgttttga atggttacca aaaaacaaac aaaaaagaa agaaaaagga aaaaaaaaaa 360
gaaaataatt gtgacatgct tttatcacta ctttattttt caaataacat gtaaataattg 420
taatccattg gattttgttt tgctaacctg ttaataaaaa tatgggacca ttatcctttt 480
aacaaggcta gaatgtcatt tttttctttt tcaacatata cctgatattt tgtggccgca 540
cattttgggt gcattattat aattckgttg actgtaatga catagaatta cacattttkt 600
gktggttaat tatacagang acattttttt canagcttga ganaanaaaa taaatagcaa 660
aatgataacc tattgactcc agtaatcagt gtttcccaat acttcataag aaatagggga 719

```

<210> 95

<211> 613

<212> DNA

<213> Homo sapiens

<400> 95

```

tattcagcta ctatacagaa aaaggatgaa caaattaatt tattttctaat tgagccagtt 60
agacataatg catataacgt gatatttggg tcatgaaaga gttgttttca tgtgggttatt 120
gtagggagta tatataattg tgggaagggg atgggaagag ttgtgtatag ttagttgtta 180
tctctacaag tttgaaagt tttccatcaa acattatcaa tataccaatg ttttaaaaaa 240
tgagtgaggg ttattatttg tatttgatga aagaaaatcc aaataaagcc cacctagaaa 300
tagatatatt attatatatg tgctatagat atacctatat agtacaaata gacatgtgtg 360
atgcatatat acaatgttat atatgtgtat atgtctgtat acacactgag tctgtaatat 420
gtatacacta aatttgtgky amgctaacak cttcaggggtc tgcactgtga actcccckgg 480
agataagtaa gtccacttta gaataaagag ttcttttgag acttcagtta ctaacgtgct 540
ttaagaggta tctactttat aactgaattc tatgtcgttc atacgtagag ttacagtaag 600
ggtctagtat gtc 613

```

<210> 96

<211> 816

<212> DNA

<213> Homo sapiens

<400> 96

```

gggaaaggag gggtcaggcg gtccacgagg aggttcgagt gaagatcaaa gacttgaatg 60
aacacattgt ttgctgccta tgcgccggct acttcgtgga tgccaccacc atcacagagt 120
gtcttcatac tttctgcaag agttgtattg tgaagtacct ccaaactagc aagtactgcc 180
ccatgtgcaa cattaagatc cacgagacac agccactgct caacctcaaa ctggaccggg 240
tcatgcagga catcgtgtat aagctgggtg ctggcttgca agacagtga gagaaacgga 300

```

53

```

ttcgggaatt ctaccagtcc cgagggttgg accgggtcac ccagcccact ggggaagagc 360
cagcactgag caacctcggc ctcccccttca gcagctttga ccactctaaa gccactact 420
atcgctatga tgagcagttg aacctgtgcc tggagcggct gagttctggc aaagacaaga 480
ataaaagcgt cctgcagAAC aagtatgtcc gatgttctgt tagagctgag gtacgccatc 540
tccggaggggt cctgtgtcac cgcttgatgc taaacctca gcatgtgcag ctcccttttg 600
acaatgaagt tctccctgat cacatgacaa tgaagcagat atggctctcc cgctgggttcg 660
gcaagccatc ccctttgctt ttacaataca gtgtgaaaga gaagaggagg ttagccaagc 720
ccccaccca tccactccc cttccctcmc cagatattta tgtgaaatga actgcagctt 780
tattttttga aataaaaact tttaaaaagc aaaaaa 816

```

```

<210> 97
<211> 577
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (38)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (575)
<223> n equals a,t,g, or c

```

```

<400> 97
cagaagccaa aaaggtctta aaattggaaa tagatgtntt tattgtactt cagccaacag 60
caagccaggg gaaggaacat acataaatat gacagggtcat atatgaaatt tggctctcct 120
cctatcaaag tagcctagga gcttggagga agcctaatta actaaaacag gaaaaaagca 180
tactcatctg atgtaaaac tcatcagctg taaattacca acattaaacc agaagtcatt 240
accagttaaa atgtgtgggt ttcattcttat tcttaaatag gagagggtggr cagtagtgta 300
agtaacattg ctttaaagrc ataaagcttk tcctggtaaa catgggtctaa atgagaaatg 360
cctccatctt ttcaggtaga accagatttc aggcatagct cagctacatc tgtatttgaa 420
atacaataaaa aatatttctt atgtctctgt attctctttt aaaaagaact gctgactggc 480
tcctgtctct tcagtaaac tgattttttt ttaaagaagt gatatgttgg actctgttgg 540
agaagaatga gcactagtat tcagccacaa gtgcnat 577

```

```

<210> 98
<211> 484
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (456)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (476)
<223> n equals a,t,g, or c

```

54

```

<400> 98
cttgcagtcc acttgctgaa gaagttgtgt catttctctg gaagaatttc caaaattctg 60
gatttttttt ttttttttga gtatttcac agctgaaaag tgattctyac tttgagtttt 120
cttcctatat ttgtatagt agttcctttt tccttcctct ttatccctcc tgttttactt 180
tatacctctc tattecttgc tcaaattatt gcaaaagcct ctatagaaag tcctctgtga 240
tctgactcct gcagactctt ccagattttt ctgcccagg cctttactga gctcaggact 300
ccagctaaat caaratackc atgttctcac ccagagtgc aaaatcctgc agataggttt 360
aagacctagt gggmtcagag cagtagctac tgggaagtta aaaggaagg gttagaaaat 420
gaatgggaca aaggcacact tctgatggag atgaancact tgaaagtgc tggtgncttt 480
ggag 484

```

```

<210> 99
<211> 441
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (328)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (331)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

```

```

<400> 99
aattcggcac agggaaaaag gctgagcgga gagccgtgct gcctggcccc tcctcaccgc 60
ccttccccgc acctcttggc tgtaccggga gcctctgaag caccggaaat gaagggtttt 120
ccaggcctgg ctcttcaacts catccttcag gggaactttg aagccatgga gacatctggc 180
tttgaggcca tggcgattcc cctgccactc tccttgctgg gataaagcca gggcgtggca 240
tcctgggatg atgttccctg ctgctgagtg tgcacacaac ctgagctcat cctgtgtacg 300
tcagctacac atgctcgcat ctaatttncc nnaacaacct agccagtact attgcttctc 360
ctcctcttac agatggggag atgatgacat atagagggtta acttatcaga gaccacacaa 420
aaaaaaaaa aaaaaactcg a 441

```

```

<210> 100
<211> 524
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (510)
<223> n equals a,t,g, or c

```

55

<400> 100

```

aaagaaaacg aaaaagaaag cccaaggcaa agaaggggga aggaaaacaa acttcgccac 60
tctytcttct ccttcctaac cttttgtyta gagcaccaca ccgctcacia actctttcca 120
aatgctcagt tggctcccaa agttggagcc tggcatgggc akggagccca caaaactcta 180
accaaactgg akgtctggcat gggagaartg cttctggttc actcttccta cctctccct 240
cctaaccctc tccttgccctg acagggagcc cctgtggcct ggactctagg ggatgccgcc 300
accagaaacc cctctgccaa tccctamctt gcacctggg aaytgcagta acttattctc 360
aaaggcttta aacacagaga tcctctcagc ggccgtgggc ctgccccctg tcctarccct 420
tgccacgttg aggggtccaa ctccaaggga caggcactgc cccaccaacg gcaaattcaa 480
aattctttca aaaaaaaaaa actgaaaacn caacccaaaa aagc 524

```

<210> 101

<211> 614

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (355)

<223> n equals a,t,g, or c

<400> 101

```

ggagaagggtt tctctctcat ctccttctcc agcaaccttg gccatggacc agccggctgg 60
cctgcagggtg gactacgtct tccgggggtgt ggagcatgcc gtgcgggtga tggtttctgg 120
gcagggtgctg gagctggarg tggaggaccg gatgacggct gaccagtggc ggggagagtt 180
cgatgctggc ttcatagaag atttgactca caagacaggg aacttcaaac agttcaacat 240
cttctgtcat atgctggagt cagccctcac tcagagtagt gagtcagtca cctggacct 300
gctgacctac acagacctgg agtccctgcg gaaccgaaga tgggggggccc ccagntcctt 360
ggcccccagg tcggcccagc tcaactccaa gcgctacctg atcctcatct actccgtgga 420
gtttgacagg attcaactacc cgtgccccct cccgtaccag ggcaagccag accccgtggt 480
tctgcagggc atcatccggt cactgaagga ggaactgggc cgcctgccc gtccctgccc 540
tggccccgtc cctcctgctg cccctggggg tctcaggtgt gtgaggccct gaccctgccc 600
tctccccagg cagt 614

```

<210> 102

<211> 544

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature
 <222> (6)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (10)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (12)
 <223> n equals a,t,g, or c

<400> 102
 cnaanntgan anaaccctca ctaaagggaa caaaagctgg agctccaccg cgggtggcggc 60
 cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagaga aaaattatTT 120
 gtatataact ttaaaaggag tagaagggtt ttttgcagag ttattacgtt tgaagtatac 180
 tttatttctt gaaaaaatta cagatttttt gtaaataatg atgtaattca actctcaaaa 240
 tatttcctac tgtttcttta ttccagttgt attcacatgt gaaagcatgt gatcagttat 300
 tgctgcatta aaacatgag tcttttttat taggtggcca ttatttatga tcttttctat 360
 gaaagagtaa ggacattaaa atgtaagatg catgatgaaa aattaagtga agaggctctt 420
 tatggttaat ttatattgaa taatgcatta ggtaggtgtt cagagtaata ttttgcgttg 480
 tgagaacatt ttttaatttta tttaaaatta aatgaaaata aattagtata ttattgtact 540
 aatt 544

<210> 103
 <211> 1887
 <212> DNA
 <213> Homo sapiens

<400> 103
 ggcacgagag gaaggaactg gtttcgggga gccctgggcg gggcggctgt ggggaggaag 60
 gtgacgtgca ggggaccaga ggctctgcac tgctcctagg acagctcatc tgtaatcaga 120
 aaaaaaataa ataaaatata gaacgctgac tcctccgtga gacagatcgg ggaccttagc 180
 actttaatcc ctcccttctg agcgctcggg gtgcactttt agactatagc tgtttcattg 240
 acgtgtcact ctccatccag tgtccttgat gtggctttta gagacttagc agaaaattcg 300
 acacaagcag gaacttgatt ttttaagaaa aaatattaca ttttgaggac attttgacaa 360
 gtaggggaag agagggttct tgttggtttg ttttggtttg ttaactaaac ctgaagtatt 420
 aattccacaa agacactgtc cctcaggacc actcaggtag agctctgcca gggacagagt 480
 ctgctagtgg gaggtctcag gtggggcggt gtgttctgtg ccatgaggca gcgacaggtc 540
 cagatggatg tcgtcaccac ctccctcagc tctcatcacc tggctcgtacg ccaggcccac 600
 ctcttcccag caagggacgc caaagaactg cagtttttat tctgagtctt aatttaactt 660
 ttcattcatct tttcctatTT tgragaattt tttgtaatta aaagcaatta ttttaaaatg 720
 tgcaagccag tatctcacia ggcattggatt tctgtggaat ttatttttat tcaaataacc 780
 atatttatct ccaggctgtg gaatcgccac tttctttgtg aagacagtgt ctctccttgt 840
 aatctcacac aggtacactg aggaggggac ggctccgtct tcacattgtg cacagatctg 900
 aggatgggat tagcgastgt gggagactgc acatccggac ctgccccatgt ctcaaaacaa 960
 acacatgtac agtggctctt tttccttctc aaacacttta ccccgagaagc aggtgggtctg 1020
 ccccgagcat aaagaaggaa aattggccat ctttcccacc tctaaattct gtaaaattat 1080
 agacttgctc aaaagattcc tttttatcat cccacgctg tgtaagtgga aagggcattg 1140

```

tggtccgtgt gtgtccagtt tacagegtct ctgcccccta gcgtgttttg tgacaatctc 1200
cctgggtgag gagtgggtgc acccagcccc gagggccagtg gttgctcggg gccttccgtg 1260
tgagttctag tgttcacttg atgccgggga atagaattag agaaaactct gacctgccgg 1320
gttccaggga ctgktggagg tggatggcag gtccgactcg accatgactt agttgtaagg 1380
gtgtgtcggc ttttycagtc tcatgtgaaa atcctcctgt ctctggcagc actgtctgca 1440
ctttcttgtt tactgtttga agggacgagt accaagccac aagaacactt cttttggcca 1500
cagcataagc tgatggtatg taaggaaccg atgggccatt aaacatgaac tgaacggtta 1560
aaagcacagt ctatggaacg ctaatggagt cagccccata agctgtttgc tttttcaggc 1620
tttggtattac atgcttttaa tttgatttta gaatctggac actttctatg aatgtaattc 1680
ggctgagaaa catgttgctg agatgcaatc ctctcgtgta tctgtatgta aatctgtgta 1740
tacaccacac gttacaactg catgagcttc ctctcgcaca agaccagctg gaactgagca 1800
tgagacgctg tcaaatacag acaaaggatt tgagatgttc tcaataaaaa gaaaatgttt 1860
cactaaaaaa aaaaaaaaaa aactcga 1887

```

```

<210> 104
<211> 253
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (226)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (228)
<223> n equals a,t,g, or c

```

```

<400> 104
agattttgaa cttaaattat attctatatg tgtatcttcc taggcaaaag ctgtaatttc 60
cagagagacc attaggaaca ggtagtatct atttlyctcc attatttatt tctagaaact 120
cataaaatgg attgtatttt tctataagaa caaaatatta attaaggat agatgactga 180
ccaagggtt aatcaaataa aatgactaac agcatctatc cataangnca cacaagcctt 240
atgttctcat ctt 253

```

```

<210> 105
<211> 705
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (671)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (688)
<223> n equals a,t,g, or c

```

58

<220>

<221> misc feature

<222> (698)

<223> n equals a,t,g, or c

<400> 105

```

cccaatctct agctagtgtt gcttatcaaa taaatgcatt ggccaacaat gtactccagt 60
tgctggatat ccaagcctct cagcttcgga gaatggagtc ttccatcaat catatctcac 120
agactgtgga tattcataag gagaaagtgg cacgaagaga gattgggtatt ttgacaacaa 180
ataagaatac atcaagaact cacaaaataa tagcacctgc gaatatggag cgccctgtaa 240
gtatatccgg aaacctatcg attacacagt tctggatgat gtggggccatg gtgtcaagtg 300
gctaaaagcc aagcatggaa ataaccagcc tgcaagaact ggcacactgt cgagaacaaa 360
tcctcctact cagaaaccgc caagtccctc catgtcaggc cggggaacac tgggacggaa 420
tactccttat aaaaccctgg aacctgttaa accccaaca gttcctaata actatatgac 480
cagtcctgct aggcttggaa gtcagcatag tccaggcagg acagcatctt taaatcagag 540
accaaggaca cacagtggaa gtagtggagg aagtgggaag ttcgaggaaa acagtggtag 600
cagtagtwtt ggcwttcccw ttgctgtgcc tacaccttcg gcaccayta ttttgaaacc 660
at ttgttgat ngttccaatt tccaccgnca ccacttttnc ccaa 705

```

<210> 106

<211> 920

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (920)

<223> n equals a,t,g, or c

<400> 106

```

gctagaagtg gattggagcc tctttgatgg atttgcagat ggggttaggag tggctgaagc 60
catttcctat gtggaccctc agttcctcac ctacatggca cttgaagaac gcctggccca 120
ggcaatggaa actgcccttg cgcacttgga gtctctcgca gtggatgtag aggtggccaa 180
tccaccagca agcaaggaga gcattgacgc tcttcccgag atcctgggtca ctgaagatca 240
tggcgagctt ggtcaggaga tgtgctgccc catctgctgt agcgaatatg tgaaggggga 300
ggtggcaact gagctgccgt gccaccacta tttccacaag ccgtgtgtgt ccatctggct 360
tcagaagtca ggcacctgcc ccgtgtgccg ctgcatgttc cctccccac tctaaagacc 420
aaggccgttt actcctggtc tgattat tttt ccccatctga aatccacaat actgcaggag 480
ccctcttgaa attaacaatg gaaataaaac caatcagtc gttagcctaa acctattgat 540
tcctcgtgat tatttccaat gtgaaaacag ttgtgtatga ttgcattaaa aatcatatca 600
tcttttagag gttagaaaag ggaaaactaa actttctaaa tgctacttga gattgcagta 660
agaagatacg ttttctaacc tgaaagttaa atcgcat tt ttttcttcag tagaatggga 720
atgtgttgct gttacttgta atgtcaagtt tatctgttaa atatgtccaa aaggcaaaat 780
catttttggt gcatgttatg ggtcgatgtt cctgtaattg cagtgccgta aaagcttatt 840
aaagtgttct ttttggtttt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900
accccggggg ggggcccggg 920

```

<210> 107

<211> 466

<212> DNA

<213> Homo sapiens

<220>
 <221> misc feature
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (7)
 <223> n equals a,t,g, or c

<400> 107
 nggccentac tcgggcgcgc ccagarggag ccacctctca gtgcctcamc tccccctgcc 60
 tcccagcctc cgcagatgag gttcctgccc cttcctctc gtaacccaaa cctcactgc 120
 tcccaggacg gtcttattta taaaccagat acatgttctt agtctgggtcc cagaccaagg 180
 agctgggtcag acggcccttt ctaatcctac atgttgagct tatgtaaaaa atgttgtttc 240
 ctctgttttt tggttccttt cttaccacaca aaccattact acttgaaaact taaaaaactc 300
 gccaaagtgt aaggctaaag agaagcagtt tgacggacct tgtgatttgt actgttttgt 360
 gcgagagctat ttaaagattt tgggaataaat atacaaaact acggttgtga aataaaaact 420
 taaattgtat attttgaaaa ataaaacact gaaaagaaac aaaaaa 466

<210> 108
 <211> 323
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (111)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (113)
 <223> n equals a,t,g, or c

<400> 108
 actatTTTTT tattttataa atctttgtag aaataagcaa tgaaatacta ctttcatctt 60
 ttgaaatggg atttttcaag gcagtgtcct tttggcatta aggtaggggg ncngttaata 120
 ttctctctgc cttgtttcca cgtggaatca atattaaagt catggacatt ttaaaatctc 180
 aatttaattt cttcttattt actatgcagt atagccgtgg aacaagtaat gtagatttag 240
 ttttctcatc ttcaaagccc ctgatcacc tacctcacag gggtgttgtg gggrrwaata 300
 aaactttatg gragcaaaaa aaa 323

<210> 109
 <211> 448
 <212> DNA
 <213> Homo sapiens

<400> 109
 ttttttcaca gcatattaga aatgtttatt aagaataatg gcatgaactg cttttaacaa 60

60

```

tttagaaaag acccattccc cccgcccsc cccgccccca gatccagggc acttcctcta 120
agtaaayaca aatattttctg tagtgaactg tatgcatatt cccactgagt aaagggttata 180
agaagcctca ggtcagggtct taccaccaa cttgaaaaca cttggaatgc agctgggcag 240
ggacttgagc aggtttttgtc ttgataagca ggtaagaatg gcagaacact ggcttattgt 300
caaccaatgt ttttttatat acctgaagta ttcacagcaa cttattttta gaagcttttt 360
aaaagttcta cacctccacc cccacaacte cccaatccag aacatggaac aagggtgtgg 420
agccgtttga tggacttggg tctgttcg 448

```

```

<210> 110
<211> 849
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (32)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (33)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (39)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (841)
<223> n equals a,t,g, or c

```

```

<400> 110
ggtgactccg tctcaaaaaa aaaaaagaag gnngtaccna cagtatacgt gtgggcactt 60
gtgcttgagc ctgtattaaa ggaatcaggc caggcacagt ggctcacgcc tgtaatctca 120
gcacattggg aggctgaggt gggcggatca cctgaggtca ggagttcaag accagcctgg 180
ccaacatggt gaaaccccat ctctactaaa aatacaaaaa ttagctaggc ggggtagtgc 240
atgcctgtaa tcccagctac tcaggagggt gaggccggag aatcgcttga gcccagagagg 300
tggagactgc agtaagccaa gatcatgcca ctgcactcca gcctgggcaa cacagggaga 360
ctccatctca aaaaaaaaaa aaaaaaaaaa aagacattca acttgaggct cctgttagtt 420
aagctatctt ctttcaacttg aagcagggtt gagaggccta ggccagaatt taaattcctt 480
ttatgaatag atttcccttt ctccctgacc ccaagggtcag aggagactat atattccatg 540
gctgcctcta agactaggaa taggaatatc tgaaaacagc atttctaagg gtggtaacca 600
caggctcgatt ttaatacgag tcctttttct tgtagaggta agtaaaatct tcctgacaag 660
gtagtcctct ttccacggca cagacaatgg gctttctgtt tatgaggggt gagaagtgat 720
gtttgttact atgttctcca gcaagtaaac attcctctgc tcacctcca acaagactaa 780
cagtcttttt agaagtaaat atattcaaga caaacgagaa aatcctggct acccaagtcg 840
ngtatatac 849

```

```

<210> 111

```

61

<211> 876
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (871)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (876)
 <223> n equals a,t,g, or c

<400> 111
 aaaaaaaatt tacaaaaaaa caamcacama aaaawtatct tttttaggcc agagttttct 60
 acagggtatta atgaatatct ttcttaatcc ttataagttt tatgtgttta atatttctta 120
 ataccggttag cattaattta tacttttgta gcaacacaat atttttataa acagccggtg 180
 cttggctcaa gtcttcacga ggggttttagg cagggccatc ttggggaccc tgtgtaccat 240
 gtactgtatt taaaaaaaaa aaaagttacc tattgtcaca cttgctgtgt taattaacaa 300
 aagatgttgt gtgcggtctc ctgtatcggt gtggatccaa cagctctcca gggagtcaca 360
 ttgcatgggg gttgagttga cggttcttgt gatatgtaaa ccccgagac caaacttgag 420
 ggtttattta gggttttctg tttgtccttt gggtttttgt ttcactttgt tttggtgccg 480
 tttctccatt tacagccaaa tcagtttcat gatgttcaaa acatttactg atgtcaaagt 540
 gaggaagga acagaaaaaa agattttttac aaagtaataa aattttaaac tgagctgttt 600
 aatgttgctg tttttacctg tctgttcttg tccaaaagtg gaacattccc agggagaaga 660
 ggaagggttc actcggttct ttaagtcgcc aaaagcccca gcccgggatt cagtacctcc 720
 cctgcccccc gaattcttgc agcactatct cccagttggt tgatgccaag gcaaaaagat 780
 aacttttaac agttagagag gatcagttgc ttaaattgatt tcatgtcagt gttgtattta 840
 tggttttaca ataaaacaac ctttaggaaa naaaan 876

<210> 112
 <211> 382
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (100)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (105)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (341)
 <223> n equals a,t,g, or c

<400> 112

```

gctctccagg ttcattgccat tctcctgcct cagcctcccg agtagctggg actacaggca 60
cctgccacca caccgggcta cttttttata ttttttagtan agacngggtt catcatgtta 120
gccaggatgg tcttgatctc ctgacctcat gatccgcca ccttggcctc ccaaagtgt 180
gggattatag gcatgagcca cegtgcctcg ctattttcag ttcttatgct gtgaaccact 240
ttgccttgta gctttttcta tctttccaaa atcctcactc tgttcattgt ttgtctcagg 300
ggaaaatctt cccccaccga gcttgtaaaa aaactttaat nattgggtgg aggataattt 360
aggatgggta tttattggag gt                                     382

```

<210> 113

<211> 1070

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (334)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (882)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (961)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1018)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1070)

<223> n equals a,t,g, or c

<400> 113

```

ggcacgaggg ccgactggac tttgtgagct ccagctgcta cagttgactg agttcaggct 60
ccatgtagct gggatatact acatgggttac ccctcacccc tatggagctt ccaaaagaga 120
ccctccctca aagcacagcc ccttctctga gtgcaataaa tggccatcag aggtcagtca 180
caggtgttag gcaggcatct atgaagctgg ggatgatagc actgacttca gtgcttggac 240
gagaaccagg agagagtgtg tagaaaaagc acagccagcc tcccataaaa ggacagaytc 300
ctgtgacaac cttgtcactc tgttcctccc tgantactct ggggagggtg aggccagtgg 360
gcagttctaa agctcagcag gtttggagcc attgggtgtg gactcctctc ccagtgttcc 420
tcctgggtgt tcacagatgt tattgaaatg cacactggga accctgcaca ggtaaaacta 480
aggytttatt ggcgtgattg ccaaagggtca cacagggtgg tttggyagag ctgggattag 540
aagcccagcc tgtytctytt cagtagtaat ggagtcctgg gaggtttact aggcttttagc 600
ctcaatctgt ggcggcaggg tccacagccc tggggagtga cacagtcatg gtccccatga 660

```

63

```

ttggccagga cctgktgtga gagacacagg agacaagacc ctgctcttcc aggccagaag 720
ggaggggagc cccagagctg ggcagtggca tgccccacag cctggccacc tgcttcggct 780
acgcaccatg cagcagctgc acctggctgc ctcgggaaaa ctctgacctc tctgggaagt 840
ggagccagtg gctctgtggg cgctctttcc tgcagcctgg anagcaaagc ggctttccct 900
gggactgtgt ggctcctgtc ccaactggcc tccccattcc acattcccat tgctggacca 960
ncaccaggac tgggcacagg gcttcctttt gctgattcat ttcccccta actcatcnaa 1020
attgaacccc atctgattcc cacatgctgg ccctgaaacg gtacaaaggn 1070

```

```

<210> 114
<211> 371
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (360)
<223> n equals a,t,g, or c

```

```

<400> 114
gtctattaga aaacggctct aagagattct ttggtgtttg gcactttaag gtcacgttg 60
ggcagaagtt tagcattaat agttgttctg aaacgtgttt tatcagggtt agagcccatg 120
ttgagtcttc ttttcatggg ttttcataat attttaaaac tttttgttta gcgatgggtt 180
tgttcgttta agtaaagggt aatcttgatg atatacataa taatctttct aaaattgtat 240
gctgaccata cttgctgtca gaataatgct aggcatatgc tttttgctaa atatgtatgt 300
acagartatt tggaagttaa gaattgatta gactagtga ttaaggagt atttgaagtn 360
gggtgggggg g 371

```

```

<210> 115
<211> 581
<212> DNA
<213> Homo sapiens

```

```

<400> 115
tttttttttt tttttttttt ttttvtgagt attccagcat tttttatttg atcagagtaa 60
aatacacttc ccatcactac aaactgagca caactacagt tgtctacaca ttcatatttt 120
tgacgtgcca acattttgca ttctacatga aacatttggg ttaaacaata tcttaagaat 180
tctctatttt gtttcccatc ttccctcctg ttctctccca tcttccaaag atgttttata 240
ttaactgcta tgagatttat ttgccgggtc cgtaatacgg aggacagcag ggaacaacac 300
aagatttacc atgcctaggg gatgaatggc aaacccaact ttggctaata tcattgagaa 360
caacttggga agcgtgasag gaggatatct catggaagtg ggcagtgaac ctacatttcc 420
atztatcaga agcaaacatg ggaagggttac atacatgatg aagtattgga agttaagac 480
ttaagacaca aaatcactaa tttaaaagra cmtgcmacmt grgtatcaac ttgctatgta 540
gkggtacatgt aaatgaccca aatattcacc tctagcatcc g 581

```

```

<210> 116
<211> 705
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature

```

64

<222> (681)

<223> n equals a,t,g, or c

<400> 116

```

atcggacggg cttaacatga aagcctatag gtcattcttg ctctgggac tacaggcagg 60
gtaggcacag gtgcagccta agaagggaac ctgcttcctc tcccttccaa agacagtgc 120
agctgactga gggcaaagag caggcaccac tcagaacgtg gtgagtacag ctgagctcag 180
cactcagtca gtggtaactt gtgcccagcc ctgtgctagg cgctgacatt aacaggagca 240
accaggggccc aattcctggc cttggagctc aaatctttcc tttgattttt gctcctgac 300
atcaaggccc cagtggcaac catgtggtaa gtggccaacc aagccctacc cagggtcacc 360
caacacactc tgccttgagc ctctcctcag ggtctattcc ttgctgggat tatgtggccg 420
tagcatgtta cagttcaaac atgtctccac taccctgtta agagcagcct gggaacgtac 480
aggccatcaa gactatttat ttaaatacaa aaaaagggga aaacacacac acggaaaaaa 540
aattgtaagc actttttttg taaaaccaat gtctgttttg ttacatacct ttcatgtcgt 600
gctttgtaaa tgtcttattt gtgtaataaa gttaatgcaa gtaaaaaaaaa aaaaaaagat 660
gggcgaagtt atcccttggt nggtaattag tttgctgcgc gttaa 705

```

<210> 117

<211> 1196

<212> DNA

<213> Homo sapiens

<400> 117

```

gcgaccgcct cgcgtacccg gcttgccggtc cagcagcgag cagccccggg gtggcgatgg 60
ggctcgcccg aggcagcgga ggttctgcgg gcgactggag gttggcagtg ggccggagaa 120
agaggaaggc aggcgcggct gggcctcggc ctctggcgcc gcggtaccct ttgtctcggc 180
agcctgacgg ccccgccggg ctctccggag aggggaacgg gcggcgaggg tggcgggtcc 240
tgggcgccct gtgctgcggg gccgagaggc gctcgggtcg cggcgggac ggccggacca 300
gacagggtta atggaagagc ctggccagtc ccgcgcgggg ccccgccagc gacagccttg 360
gccgcgggga ctggagtcct gagggggaga agcctgccgt tctgaaggct cgggacttct 420
gccccaaaga cttcgccgcc gagaactgcg ggtgcactgc ctcagggaag aagttgagaa 480
ttttgccagg tcatctctgc cagggcacag ttcatcactg tgtgtttagt gtgtttcggt 540
gaagctctcc aagtgtgttg aatcagcgtg cctagcctca agggtgcac gtgaaaactg 600
aaaccaaagg aatgatacag gcctgctttg tgtgtgtctt cccactttta gcttgttttc 660
agtacaaata ctcttgcttt aaacctgatt ggactgtggc gagcggacat ctgttcaaag 720
gagggggccg gaccacagta cttctgaagg gggcttgata atgtggaaac attttaagtt 780
ttctctccgg actgttttgc tctctcaatt caggcaagtt actgaagtac gttttttatc 840
tagaaaaagg tttgatgtag tctgtaaatt gtccttgtaa agtacattgc catctcagaa 900
ttaaaagatc cactctcatt tattatgcag aagttagtgg tcattctttc ctgtagatag 960
tttatctcat gtaaagaccc acccagcttg gtttaaattt ttttctcact gacgtataac 1020
catcagcttt gatacttcca ttttcaggct cagacttttg attttaaggaa actaaagatg 1080
actttatttt cttttctctt ggtttttttt ttccaaaaac aaaaaataaa tccattacat 1140
gttaacataa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaacggacgc gtgggc 1196

```

<210> 118

<211> 975

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

65

<222> (794)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (845)

<223> n equals a,t,g, or c

<400> 118

```

tgtccctttt tattctagag gcttttcctt taattcagag attagtggag ataataacgt 60
cagtcaaggc taatgtggta catggaactt gctaattggag gttggacatt ctgtttcagt 120
cttacatgga tattgtttca ttggtgttga ggaagaaaaa aattagatac taccatgcat 180
tgggacagca taattcctaat attacattga atatggcttt ttaaaaaataa gtattaaaaa 240
gccaatcggt ttctccattt atctatcttt tttgtttgtt ttttaatttgg ttgattgata 300
tgcacccagg ccgtcttatt tttacttggt aaatgtctgt ctaggaagaa ctgtgattgg 360
aaaggaatta attattatac aaataaatct ggtaggatat gagtggagta agtttgcttg 420
aaacagaagt atatttttcta ctttgaatca cctcaccaga gtcactctgtc aagaattatg 480
tataacaatt tatcttttatt gcctacatac aacatacttt ttctgaatta agataacttc 540
tattttgtgag ttgaacttca ttatctgcca ttttgtggaa tcaaccttac attytttgggt 600
ggractagag ctgattgtca ccacaagggt atatgacaac tctgttctar grettatacc 660
yattatatag ggktatacct tttttcttat gcctcagctc tgtacctgac aatttatgat 720
tcagtggagc caagctagaa ggaacaaagg tcatctaaca ctgtgatggg gatgaattcc 780
tgagtttttac ctgnacaatg aggtgggtgcc ccggaattca caacagagta gtgatagagc 840
ataangatgg ctgctccaga tgactcttgg gtttaagtgt acttgtgatt gaacaagatt 900
tttatctatg aagcttgatt ctacaaccaa aataatagaa atggggggggg ggggaatcat 960
gtctgcttat gctttt                                     975

```

<210> 119

<211> 331

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<400> 119

```

catatattag tgtgctttga agttgactga aagatatact ggatatcata attatataat 60
ttctaaatag atttctttta atccatgcta tgttttcttt ttcagtcagg tcctacagaa 120
tgactattgc acttgggtcta ttgttttaat agtaaatttt gttattaatc tcctatgtgt 180
taaacgtggg taattgtatt atgttaatac atacttaggg aggaaaagca ggtggatgta 240
aatcagtgat tcccaacttc agcagatggw tagcmgtggg aggggtatcct tggagctttt 300
tgtaaatatt tccaaaaaag gggggggggg n                                     331

```

<210> 120

<211> 233

<212> DNA

<213> Homo sapiens

<400> 120

66

```

tcgacccacg cgtccgcccc cgcgtccgca aaactgagag ggataggaaa gaaaaactta 60
tccaggaagg aaaattggat cgaacatttc acctctcata ttaagtctgg caatgatgac 120
tatatgtatt cctgcctaaa taaatcatct attaatcatt aaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg ggg 233

```

```

<210> 121
<211> 2043
<212> DNA
<213> Homo sapiens

```

```

<400> 121
ggcagcagca gccctcggcc ccaccctac gaccagcct tccgtcctgc ccaccccggc 60
agcgactggg gttcctgaag acacataaat ccgggagcag ctctgtgctg agcctgcttc 120
accgctatgg ggaccagcac gggctgcgct tcgccctccc tgcccgtac cagtttggtc 180
acccaaagct cttccaggcc tctagggtaa aaggctaccg cccacagggt ggaggcacc 240
agctcccttc ccacatcttc tgtcaccaca tgaggttcaa cctgaaagag gtacttcagg 300
tcatgccttc tgacagcttc tttttttcca ttgtccgaga cccagcgggt ctggctcgtc 360
ctgccttctc ctactataaa tccacctcat cagccttccg caagtcacca tctttggctg 420
ccttctctgg caatcctcga ggcttctaca ggctggggc ccgtggggac cactacgctc 480
gcaacttact atggtttgac tttggcctgc cttttcccc agagaagagg gccaaagagag 540
ggaatatcca tccccccaga gaccccaacc cccacagct gcaggctctg ctttctgggtg 600
ctggccctcg agcccaaacc ctcaatccca atgccctcat ccaccctgtt tccactgtta 660
ctgatcatcg cagccagata tcaagccctg cctctttcga tttgggggtc tcatccttca 720
tccagtgggg tctggcatgg ctggactctg tctttgacct ggtcatggtg gctgagtact 780
tcgatgagtc attggttctg ctggcagatg ccctgtgctg ggggtctagat gacgtgggtg 840
gcttcatgca caatgcccgag gctggacata agcagggcct cagcactgtc agcaacagtg 900
gactgactgc ggaggaccgg cagctgactg caccggcccg agcctggaac aacctggact 960
gggctctcta tgtccacttc aaccgcagtc tctgggcacg gatagagaaa tacggccagg 1020
gccggctgca gacagctgtg gccgagctcc gggctcgccg agaggcccta gcgaaacatt 1080
gtctggtagg ggggtgaggct tctgacccca aatacatcac tgatcgccgg ttcgccccct 1140
tccagtttgg gtcagctaa gttttgggct atatacttcg gagtggattg agcccccaag 1200
accaagagga atgtgagcgc ctagtacccc ctgagctcca gtacaaggac aagctggatg 1260
ccaagcagtt cccccctacc gtctcactgc cctcaagac ttcaaggcca ctctccccat 1320
aaacatcaga ctacagattt aggtggaaga gcagccatgt ttgaaggcca catgtgatga 1380
gtggggggca gcaagatgcc atttctgcat ctcccagaag ggatgagtct ttgtcccaaa 1440
tgcaagcccc ctcttcgctg ggctcccagc agtgcctccc tcctccacc tccactcatt 1500
ttgttctttc ccccactt tttttttttt ttgaaacgga gtcttgcctc gtcccccagg 1560
ctggagtgcg gtggcatgat ctgggctcac tgcaacctct gcctcccagg ttcaagcgat 1620
tctcctgcct cagcctccag agtagctagg attacagata cgtgccacca taccgggcta 1680
atttttatat ttttagagac agggattcaa catgttgggt aggctgggtc tgaactcctc 1740
acctcaggtg atccacatga ctctgcctcc caaagtgtc ccattacagg cgtgagccac 1800
taggcctgac ctcccccttc cctttcctgc cccaaggcag atccacatca ccgaagctcc 1860
ctagaggggc aaaagatgga gtgagccaca ggaagtttgg ggcgtggtga gttggaatga 1920
tacgtccatt tctctatgaa atatttgcct ctagactgtt catttctctc tgacatgttt 1980
gttgaatgaa taataatatt gaaacttcaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2040
aaa 2043

```

```

<210> 122
<211> 2877
<212> DNA
<213> Homo sapiens

```


<400> 122

```

tcgacccacg cgctccgggat gagggccggc ctctcatttc tccctagccct tctgtttcttc 60
cttggccaaag ctgcagggga tttgggggat gtgggacctc caattcccag ccccggttc 120
agctctttcc caggtgttga ctccagctcc agcttcagct ccagctccag gtcgggctcc 180
agctccagcc gcagcttagg cagcggaggt tctgtgtccc agttgttttc caatttcacc 240
ggctccgtgg atgaccgtgg gacctgccag tgctctgttt cctgccaga caccaccttt 300
cccgtggaca gagtggaacg cttggaattc acagctcatg ttctttctca gaagtttgag 360
aaagaacttt ccaaagttag ggaatatgtc caattaatta gtgtgtatga aaagaaactg 420
ttaaacctaa ctgtccgaat tgacatcatg gagaaggata ccatttctta cactgaactg 480
gacttcgagc tgatcaagggt agaagtgaag gagatggaaa aactggtcat acagctgaag 540
gagagttttg gtggaagctc agaaattgtt gaccagctgg aggtggagat aagaaatatg 600
actctcttgg tagagaagct tgagacacta gacaaaaaca atgtccttgc cattcgccga 660
gaaatcgtgg ctctgaagac caagctgaaa gatgtgaggc ctctaaagat caaaacaccc 720
ctgtcgtcca cctcctccc actccaggga ctgtggtcat ggtggtgtgg tgaacatcag 780
caaacctgtc gtggttcagc tcaactggag agggttttct tatctatatg gtgcttgggg 840
tagggattac tctcccagc atccaaacaa aggactgtat tgggtggcgc cattgaatac 900
agatgggaga ctgttgaggt attatagact gtacaacaca ctggatgatt tgctattgta 960
tataaatgct cgagagttag ggatcaccta tggccaagggt agtggtagag cagtttacaa 1020
caacaacatg tacgtcaaca tgtacaacac cgggaatatt gccagagtta acctgaccac 1080
caacacgatt gctgtaactc aaactctccc taatgctgcc tataataacc gcttttaata 1140
tgctaattgtt gcttggcaag atattgaact ttctgtggat gagaatggat tgtgggttat 1200
ttattcaact gaagccagca ctggtaacat ggtgattagt aaactcaatg acaccacact 1260
tcaggtgctt aaacacttgg tataccaggc agtataaacc atctgcttct aacgccttca 1320
tgggtatgtg ggttctgtat gccacccgta ctatgaacac cagaacagaa gagatttttt 1380
actattatga cacaaacaca gggaaagagg gcaaaactaga cattgtaatg cataagatgc 1440
aggaaaaagt gcagagcatt aactataacc cttttgacca gaaactttat gtctataacg 1500
atggttacct tctgaattat gatctttctg tcttgcagaa gccccagtaa gctgttttag 1560
agttaggggt aaagagaaaa tgtttgttga aaaaatagtc ttctccactt acttagatat 1620
ctgcaggggt gtctaaaagt gtgttcattt tgcagcaatg tttagggtgca tagttctacc 1680
acactagaga tctaggacat ttgtcttgat ttggtgagtt ctcttgggaa tcatctgcct 1740
cttcaggcgc attttgcaat aaagtctgtc taggggtggga ttgtcagagg tctaggggca 1800
ctgtggggct agtgaagcct actgtgagga ggcttcaacta gaagccttaa attaggaatt 1860
aaggaaacta aaactcagta tggcgtctag ggattctttg tacaggaaat attgcccatt 1920
gactagtcct catccatgta gcaccactaa ttcttccatg cctggaagaa acctggggac 1980
ttagttaggt agattaatat ctggagctcc tccaggggacc aaatctccaa cttttttttc 2040
cctcacttag cacctggaat gatgctttgt atgtggcaga taagtaaatt tggcatgctt 2100
atataattcta catctgtaaa gtgctgagtt ttatggagag aggccttttt atgcattaaa 2160
ttgtacatgg caaataaaat ccagaaggat ctgtagatga ggcacctgct ttttcttttc 2220
tctcattgtc caccttacta aaagtcagta gaatcttcta cctcataact tcttccaaa 2280
ggcagctcag aagattagaa ccagacttac taaccaattc cccccccac caacccctt 2340
ctactgccta ctttaaaaaa attaatagtt ttctatggaa ctgatctaag attagaaaaa 2400
ttaattttct ttaatttcat tatgaacttt tatttacatg actctaagac tataagaaaa 2460
tctgatggca gtgacaaagt gctagcattt attgttatct aataaagacc ttggagcata 2520
tgtgcaactt atgagtgtat cagttgttgc atgtaatttt tgcccttgtt taagcctgga 2580
acttgtaaga aaatgaaaat ttaatttttt tttctaggac gagctataga aaagctattg 2640
agagtatcta gttaatcagt gcagtagttg gaaaccttgc tgggtgtatgt gatgtgcttc 2700
tgtgcttttg aatgacttta tcatctagtc tttgtctatt tttcctttga tgttcaagtc 2760
ctagtctata ggattggcag tttaaatgct ttactcccc ttttaaaata aatgattaaa 2820
atgtgctttg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 2877

```

68

<210> 123
 <211> 681
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (101)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (223)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (224)
 <223> n equals a,t,g, or c

<400> 123
 ctccctctcc cttttgctgc aagactggat ctgctcttga atctgccccg gataattctg 60
 ggcagcttct tcgatcaagc tgacattatg ggatttgtgg nccttggatt cacgacacac 120
 aaaacagagg aacttcccat catcctcgca gaaatagtgg aacatctcct ggtgcctcgg 180
 gcaatgtagc ctcttttctt tttggactgc acctcagagg ctngtagag ctttggattt 240
 tctccaccag attccgcaac agcgagttga acctgattgc gttcttctctt acggaagttt 300
 tgcagagggg acatttgaaa aatccacatg atgtttcccc aatctgagtg atgcatttga 360
 ggcagaaatt gtgcccacag tcgatgggtga caggtttctg cagaatgtcc aggcagatgg 420
 ggcagatcac ttctctttgc agtttgttca caaactgccc actggccatg acagaacaac 480
 agggctgttt caagactgta ggaagctgtg ccaagtctgt aggagccccg gagtccactg 540
 tggatactgt ttctaggaag ggagaaggga gtcagagaaa gtggagggtca gagattctgc 600
 ccaattagtt agaagagcag agagagagga aaagaagagg gagaaaaaaa taaagaaatg 660
 atagaaaagc gtaaaattta g 681

<210> 124
 <211> 606
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (34)
 <223> n equals a,t,g, or c

<400> 124
 ttgatggcca tttggaagta aatttccgca gtanttcata ggtgcactta acacagactt 60
 tgcttaaatga aaatgtcagt tctaatagta actgattcac ttctgaacag aagtgatttt 120
 aggcataattt cttaacatat atcaagcaaa gtcctgttaa aagatctaaa tgaagaatgg 180
 agacctcagt gattaaagat attttgtttc tgaccttgag cagattgctt acctgttctc 240
 tagactataa cccaacatgt aaaaaaaatt tgaagatggg gatgaggaaa gtgagatata 300
 tatatatata tgtattaygt ttctagcact tttccctttt aaaaagtgaa aatatccttg 360

69

```

tacattttttg aaaaatatat ttycagtyct gaaaaatgta gcagaagtag tgaaaatgyc 420
atatttttaaa tgttgattat tagataaatt taacctgctt agggtttatt gtaactacac 480
ctttcagacg tgtgttttygg agtagtggaa ttgccagcca ggcctgtgg cttggaaagg 540
catcccagaa atcctcggcc agaaggtgtg gcttgttaaa gcattgagat tcmgagtatt 600
ttggtt                                     606

```

```

<210> 125
<211> 1211
<212> DNA
<213> Homo sapiens

```

```

<400> 125
aattcggcac gagagcggcc ttcctcggtc aagtcgctgc gctccgagcg tctgatccgt 60
acctcgctgg acctggagtt agacctgcag gcgacaagaa cctggcacag ccaaytgacc 120
caggagatct cgggtgctgaa ggagctcaag gagcagctgg aacaagccaa gagccacggg 180
gagaaggagc tgccacagtg gttgcgtgag gacgagcgtt tccgcctgct gctgaggatg 240
ctggagaagc ggatggaccg agcggacaca aggggtgagct tcagacagac aagatgatga 300
gggcagctgc caaggatgtg cacaggctcc gaggccagag ctgtaaggaa cccccagaag 360
ttcagtcctt cagggagaag atggcatttt tcacccggcc tcggatgaat atcccagctc 420
tctctgcaga tgacgtctaa tcgccagaaa agtatttcct ttgttccact gaccaggctg 480
tgaacattga ctgtggctaa agttattttat gtggtgttat atgaaggtag tgagtcacaa 540
gtcctctagt gctcttggtg gtttgaagat gaaccgactt tttagtttgg gtctactgt 600
tgttattaaa aacagaacaa aaacaaaaca cacacacaca caaaaacaga aacaaaaaaa 660
accagcatta aaataataag attgtatagt ttgtatattt aggagtgtat ttttgggaaa 720
gaaaatttaa atgaactaaa gcagtattga gttgctgctc ttcttaaaat cgttttagatt 780
ttttttgggt tgtacagctc caccttttag aggtcttact gcaataagaa gtaatgcctg 840
ggggacggta atcctaatag gacgtcccg ccttggtcaca gtacagctaa tttttcctag 900
ttaacatatt ttgtacaata ttaaaaaaat gcacagaaac cattgggggg gattcagagg 960
tgcattccac gatcttcttg agctgtgacg tgttttttatg tggctgcca acgtggagcg 1020
ggcagtgtga taggctgggt gggctaagca gcctagtcta tgtgggtgac aggccacgct 1080
ggtctcagat gcccagtga gccactaaca tgagttaggg gagggctgtg ggggaactcca 1140
ttcagtttta tctccatcaa taaagtggcc tttcaaaaag aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa a                                     1211

```

```

<210> 126
<211> 881
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (7)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature

```

<222> (34)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (37)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (41)
 <223> n equals a,t,g, or c

<400> 126
 tatgatncct cgctcngttt ctgaaatttt cacnttnac naggtttcaa catataaact 60
 ttcaggggac acagacattc agactatagc accaagctgt agaagctaca tagttgtaga 120
 ccaggggtcag caacccaaga agcctgactt ccaagctgtg cttttaactt cccaccatg 180
 ttgcacctaa agctttggag ttttcctgtg attagtgttt ttggtgttgt tttatttttt 240
 ttcttacagg aactcttgca agaagaaagg actatgrgkt cmaactttaga gggasccatg 300
 gggmctaaac maaatttcka ggccccctca accatctaaa tggacttcct tctgggccag 360
 gacactcgaa aattaaacct gaaagactgg ttcaggccat gatgggaagt gggagtcgaa 420
 catgcctcat cataccctcc agcattaaca tcaacacaga ccttaaggct gataagaagc 480
 atttacaatc tattctctct gaagtcttct acctggaggc ttcactctgca tgataaaaact 540
 ttggtctcca caacctctta caaccaggc attcctttct atcgataatt actctttcaa 600
 ccaattgcca atcagaaaat tggttatatc acctataatc tagaagcccc cacatcaagt 660
 tgttttgcct ttctggacag gaccaatgta tatcttaaat gtatttgatt gatctctcat 720
 gtctccctaa aatgtataaa accacgctgt tccccgacca cctggagcac atgttctcag 780
 ggtctcctga gggctgtgtc acaggccatg ttcacttaca tttggctcag aataaatctc 840
 ttcaaatatt ttaaaaaaaaa aaaaaaaaaa aaaaaactcg a 881

<210> 127
 <211> 917
 <212> DNA
 <213> Homo sapiens

<400> 127
 ccattctcac attttgettc catatttgaa gagtctcacg tgccagtaat tgaagaatct 60
 ttgagagttc agatatgtga aaaggcagaa gaattaaagg acattgtgcc tgaaaagaaa 120
 agcactttta atgaaaatca gcctgagata aagcatcagt ctcttctcca gaaaaatgtg 180
 agtaagaggg atccaccagc cagtcattggg cacagtaaca agaaaaatct attaaaagta 240
 gaaaatgggt ttacacgaag aggtagatcg gttagtccca aaaagccagc cagtcaacat 300
 tcagaggaac atttggataa gattcctagt cctctaaaaa ataaccceaa aagaagacct 360
 agagatcaat cctcagccc cagcaaaggg gaaaataaaa gttgtcaggc cagcaccagg 420
 gcaggctctg gacaagatca gtgcagaaaa agcagagtcg tcgccagccc aaaaaagcag 480
 caaaaaattg aaggaagcaa agctccatca aatgctgagg ccaaattatt agagggtaag 540
 agtcgaagaa tagcaggcta tacgggcagt aatgctgagc agatcccaga tgggaaggaa 600
 aatcagacg tcatcaggaa agatgcaaag cagaatcagt tggaaaaaag cagaacaagg 660
 tctccagaga aaaaaatcaa aagaatggtt gagaaatctc tccatccaa aatgactaat 720
 aagactacaa gtaagaaggt atctgaaaat gaaaaaggaa agaaagtaac cacaggagaa 780
 acaagttcta gtaacgataa aataggagaa aatgtccagc tatcagaaaa gaggctgaag 840
 caagaacctg aagagaaggt agtttcaaac aaacagaaag atcacaagg gaaagaacta 900

gaggcagctg tacaaaa

917

<210> 128

<211> 1287

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1142)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1233)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1265)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1271)

<223> n equals a,t,g, or c

<400> 128

```

tttaaaaacc cctggagggt ttaaccttgt gatgccttta tgaatatacct gttgaaatat 60
ccttccccct atgccttata aaccagagaa agccctttga agccttataa tgccaatgga 120
agatacttag aagtaaacaa aatagagagg tatatgtaga ttttcttagg tcattagttt 180
gtgtctttgt ctggtaggct gaaactactg tcatatgact ctctccctgg ccagatttta 240
atagtcatac taatactgat gtgaatcctg ataattaaac tatcttgtca ttacatttgt 300
agataaagtt ttggttagaa atgattttgt atgtgttagg tatggtaata cagtctcaaa 360
taaaagggtca tgttaagata aaagggtcatg cttacttttt aattaatttg tgtaataaaa 420
tttaggtctt tggaaaactt atttttcaaa taaatgaacc tttcaaataa aaaagagaat 480
tagtttaacc tttatctcat ttcctattat aggggtattg aatggacaag ttgactagt 540
tttctttctt ttgctacctc aacaccaaac aatatgggat tagtgagaaa tgaacttcaa 600
ctggttgata ttccaacagg tttgttttta aagatccaaa taggtttgtc atattgaata 660
aacatgttgc catttataaa acatgtttga aagtacttct ttcaccttgg aatttttttt 720
tatatttcat gcttatatat ttatyccttt attctcctaat aattgcccta gaaaggcctc 780
atcattgttt acatggaaat gttgttggca caaatacatg gtaaaatgga ggaccattag 840
cctgaamaga cagattcatt aaaaaatagg ataccggttc tacttttaag tgcattgtta 900
tatgtaacca actttaaaag atcgatttaa aaataactct gtcaatggac tttattagag 960
tctgtgctgg aaatttttggc ttttatagga aacacttaga aaattttatag gtttaaggatt 1020
gttttttaaa gctcaaatat aaaacttgta atagtctctg gcygaatgga atagagaaac 1080
ttaatttggg atttttgaaga ttctacagta ggaaacgtcc ccaataaggk aactttttca 1140
gnaattggaa agcctaaacc ccagtgaatt tccaaaataa rgaatttggg aaattataaa 1200
gggraagrpg ttccaaatta ttttcctggg ggnatgcagg aagggtccaa aagagggttt 1260
ttttnaaaat nacaattgtg atgaggt 1287

```

<210> 129
 <211> 603
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (391)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (517)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (580)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (602)
 <223> n equals a,t,g, or c

<400> 129
 cgcttgggct tggcggggtat aggttgcaagt gagccaagat ggtgccactg cactgcagcc 60
 tgggtgggctg aacgagactc cgtctcaaaa aaaaaatcta aatctgacat ttgatgctat 120
 ttttattaat attggaatgt tctgtcttga actttattca atataatcaa gaataaagat 180
 agagtaaacg tcaactgattt gtactattaa gagagaaaaa atatgccaca caactaaaca 240
 taggtttaaa ttatgaagaa atttagaata gaggtttatt agatttaggg aacactaaga 300
 acaaaaaagg aaggagtgat acctgcctga gtggacagct gtaaatacagc tgtaattact 360
 gcagttgtwc caatagttgt gartggctcc nagtcmcttt argagtcctt ggaartwctt 420
 ggtacacatt tgttggctgt wccttaaagg aartggcaar tccagtttgt tcyctctacc 480
 acactaract gccactgaca agtttgggtc tgttggnttc aaaattttgt aagccatttt 540
 cacaagtaca aagatacatt ttaaccttgt ctctccaan attactgagt aggaatttta 600
 tnt 603

<210> 130
 <211> 532
 <212> DNA
 <213> Homo sapiens

<400> 130
 ccacgcggtc cgaagagagg ttggtagaaa aactaaaact ctacaatcta tttcttaaaa 60
 ataatgtttt tcttttcttt ctttcctttc ttttctttct tttctttact tttttttttc 120
 ttttcttttc tttttttttt tttgacaggg tctggctcta tagtccaggt tgagtacagt 180
 ggtgtgatca cggctcactg caaccttaac ctctaggctc aagtgaccca cctcagcctc 240
 ttgagtagct gggaccacag acacaccacc atggccagat agttttctgt attttttctt 300
 tgtagagaca gggtttcacc atgttgccca ggctgggtctc aaactcctga gctcatgtga 360
 tctgcctgcc tcggcctccc aaagtgtgtg gattacaggc atgagccacc acatgtggcc 420

cattttttct tcataagtga gttttagtgg tttactttgt tctaattttt tgaggctatg 480
 ttcaggaagc catcacagctt gaataagtaa ccatctcagg agaaaaaaaa aa 532

<210> 131
 <211> 776
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (630)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (669)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (769)
 <223> n equals a,t,g, or c

<400> 131
 aatcctcagc cattttgtga aaatagccaa gaaacttcta gaactcaaca accttcattc 60
 tctcatgtct gtgggtatcag cattacaaag tgctcccatc ttcaggctga caaaaacctg 120
 ggctctttta aatcgaaaag aagactacct ttgagaaatt ggataacctga tgtcgaaaga 180
 agrtaattac aagcggacac gggaatatat ccgargcctg aagrtgggtc caagtattcc 240
 ctatctagga atctatcttc tggrrtttaat ctacattgrt tctgcatatc ctgcctcagg 300
 agtaatcatg gaaaatgaac aaagatccaa tcagatgaac aatattcttc gaataattgc 360
 tgattttacaa gtttcctgca gctatgatca cctcaccacc ctgccccatg tgcagaagta 420
 cctgaagtcc gtacgctaca ttgaagagct ccagaagttt gtggaagacg acaactacaa 480
 actgtcgctc agaatcgaac caggaagcag ctctccaaga ctagtctctt ccaaggaaga 540
 tcttgcagggt ccctctgctg gctccgggtc tgcgagggtc agccggaggc acctgtcctg 600
 acacatctgt tgctggcagc ctccccacan ctccagtgcc cagacacagg gaagagccac 660
 agcctaggna acaatatgga tgtgttcagt tgagtgttag ttgaggagta aaagtgcgac 720
 atttcccttc ggagaaaggc aagggcacct acttggacga cagtgttcnt agagtt 776

<210> 132
 <211> 689
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (348)
 <223> n equals a,t,g, or c

<400> 132
 atcagggacc cttttgatcc aattatagtt attgggcaga tacagtagta ccctattatc 60
 agaagaccta gtttcaaadc ctgagtcaat ttctaattca ctgtgtgacc ttgtacaagt 120

```
cacttaagct ctctgatcat tggttcaaca tctttaatat gaggagagta atgcctatct 180
caattacctc ataaaattat tgcaaagatc aagtgagttg atatgttaca aattatttct 240
aaattataag attctgtata agtggaaggg ttaagtatac tcccatatta ttaaaccacc 300
tacgtatcac tcaggattct atatgactct gagttctcaa tttctagnaa atgggtcccat 360
ttttgctttg ttccctacaa ttctacggag tctttttttt ttwaaaggaa ggggtgtaggc 420
aaaggtaaat gggagaaaaac atggaatcac ataccactct ttggtgctgc taggcaagaa 480
ttttaaactg agtttaggtc accatcgtgg acttaagggtc catatcacct caggagagaca 540
agtagagtgg gaggcaccca aaaggtaggt gattcttctc ccctctagtg aagaatacaa 600
ggtcaattta caaaaaagca ccagcagcaa ataattggaa aattaaattc ataaamcatt 660
tataatagcg tcaaaaaaaaa aaaaaaaaaa 689
```

<210> 133

<211> 555

<212> DNA

<213> Homo sapiens.

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (36)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (308)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (484)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (489)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (510)

<223> n equals a,t,g, or c

75

<400> 133

```

ttcntgccccg ccccatcctg tgctttggcg taggcnatca ctgaagactt tctattttctc 60
cattagttca ttcattttgg tagctagact catgacggag ctgctgccac cccagcagat 120
ctgctcgect tgctgcttct tcacgggtctc cacggccttc gcagaggtgt cagcaactgc 180
catgaccact tgcagcagtt ggctgtagga agtcagattc tgggtgctgg cctggatgat 240
ggggccgcac ggggtggaggc cagggcctgg gcgctggcag cactcgccca gctcgctctc 300
gtagattngg agaaaagcca agattagctg gtggaagtcg gaagtgacca gacgcagctt 360
ctgggtctagg gtgctgatgt cggctgcgcc cgcaaacccc cttgcttcat gctgtgcaaa 420
ktactccgtt tctaaagcgc gtgcaattgg gcagcattct cctggcagtg nctgggcaac 480
ttcngccanc tttttcttct tcttcggaan ttggcaaagg catgggcccc atggccatca 540
tcaatctggc ttgtt                                     555

```

<210> 134

<211> 790

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (776)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (780)

<223> n equals a,t,g, or c

<400> 134

```

gcaagaatat aaaattctga ggccatatttt agctctaagc cagaccatgt tataactttct 60
taactgaata cttcttatct atactttttt tctatatctt tccatctatc tgtaagtagc 120
ttttcccatg atctgacttg tttatatattc ctattaactg acaaagcatt taaaaacagt 180
taaaaattgt ctgcagaggc atttttaaag tcaagacatt ataaaatact ttagattttat 240
acagcaattg tgaacacctt tgacaaatga acatgtctgt tcagcctttt tggtagccct 300
ttttattttg cttaggtaga tcaaattcta agttgatctt ttctagcagc aggggtcagag 360
tctagtgtac gtttttataaa tggcttagat gctacctttc ttttctgaga actcagtgtg 420
atataatcct tataagatat tgacagctaa ttttatggat tatcctaccg ggacagtgga 480
acctaagtag tttgaagacg araaatttgt ttgattcaka agcaatgggt tcaactagtga 540
aaggaaagat cccacgatcg taagtggtaa atgtttatat ttgttgaata actctctgaa 600
aaaaggaaat aaagtagatt agccttggta agaggtggct taagagtggg tttatgaatc 660
taagttttat ttgaaaaatg tgtgaacttg ttttaaggtaa atgtgagaat taataaagga 720
attgagaaga aagatatattg atcgtttttt ggaataacat ttaccaat taagangtn 780
aactactttt                                     790

```

<210> 135

<211> 1408

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (116)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1364)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1381)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1393)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1399)

<223> n equals a,t,g, or c

<400> 135

```

tttgccagct ctgaatcttt attttaattg atctttttat tgatgtgtta tataaatgag 60
gaagaaaaat tttgtctgat tatgtgaagg atctttctgt acatgaaaag aagggnaaat 120
aaacttgcaa ttgaatagac tgattatagt agcactgaga cacaaaaaga ttgaccatgt 180
tgccctccag acactcatac aaggtcgtgg acaccagggt gaaggcggac tatttagggg 240
ggtaaaggaa ttatgattgt tcttgagcca aagtaattta gtttgaatat aatgaaacat 300
accctgtaaa gactgctaga aagtaaaagg attcgtcttc agagggttgta gaagggtgcc 360
ttcttagtta aaaccaaact gggaaaagta atactggata aaatattcag gataaatttt 420
gcctcagcag aatttcaaag ggcagttggt cctctgtttc attattgaat sttcagaata 480
tagttaaagc caaargctta aaatatgtta aatgtttcac ttataaccat aatcttttta 540
catagagcat actctgcctt cataataact aaatcctctg catgtggtag atgagtacgt 600
ttaggaaata ttgtcagtg cattaatatgg cctacacttt aaacagtatc ataaaaacaa 660
atccttaaat atattctact tgagtcacaa aagctgaaca acagaaagggt gttttgtttt 720
tgcccttctc acagtgttgt ggtgagaatc agatgagata gtatttkgac taaacacttc 780
tgaaattgta aatatatggg ggcattattg ttcttatgtc ggcttaggag gataccaaaag 840
gggaagttaa tggtcacagt gcacttatgt agctttctaa gctactcaat gtgattcttg 900
ttctctttgc tgttcttttt ctcctcccc atgggtgtcct tcagagagaa aaggaatgta 960
gataaatgaa tccctgcaga tgtgtcctga catttcaggg agggacaggg tataatgatg 1020
ccatcctgca aaggcagcct gtgtgagaaa aagaaatcaa ataagtggg ttttaaaatt 1080
acaaaagaca ttcatTTTgca gtttatgaaa ggaaaatgta gtttggatac aaagctgatt 1140
aaattggatc aagaaatatt agaattaaat gcaaaaaata atccatgcat ttatggTTTT 1200
gatttttata tattcccagc tagttgaaaa tggatgattc ccacaagaag cataactcag 1260
cttggttccct gcttaccgga gtatttccac tatggtatat attgatacat tccttccatt 1320
atggtagggt gtataccaga ggtaccagtt accggtgggg atcntaattg gaattttggc 1380
ncccggggtt ccngggganc ctttaciaa 1408

```

<210> 136

<211> 902

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (902)

<223> n equals a,t,g, or c

<400> 136

```

aattcggtt tcgagcggtc gcccggtcag gtacttataa ttttggcctt ctgcactact 60
cttttgcctt tacgaacata atggactcct aagaatggaa agggatgaca tttacctatg 120
tgtgctgcct cattcctggt gaagcaactg ctacttgctt tctatgcctc taaaatgatg 180
ctgttttctc tgctaaagggt aaaagaaaag aaaaaatagt tggaaaataa gacatgcaac 240
ttgatgtgct tttgagtaaa tttatgcagc agaaactata caatgaagga agaattctat 300
ggaaattaca aatccaaaac tctatgatga tgtcttccta gggagtagag aaaggcagtg 360
aaatggcagt tagaccaaca gaggttgaa ggattcaagt acaagtaata ttttgtataa 420
aacatagcag tttaggtccc cataatcctc aaaaatagtc acaaataa caaagttcat 480
tgttttaggg tttttaaaaa acgtgttgta cctaaggcca tacttactct tctatgctat 540
cactgcaaag gggtgatatg tatgtattat ataaaaaaaa aaaccttaa tgcactgtta 600
tctcctaaat atttagtaaa ttaatactat ttaatttttt taaagatttg tctgtgtaga 660
cactaaaagt attacacaaa atctggactg aagggtgctt ttttaacaac aatttaaagt 720
actttttata tatgttatgt agtatatcct ttctaaactg cctagtttgt atattcctat 780
aattcctatt tgtgaagtgt acctgttctt gtcncttttt tcagtcattt tctgcacgca 840
tcccccttta tatggttata gagatgactg tagctttcgt gctccactgc gaggtttgtg 900
cn 902

```

<210> 137

<211> 730

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (606)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (647)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (671)

<223> n equals a,t,g, or c

<220>

78

<221> misc feature

<222> (685)

<223> n equals a,t,g, or c

<400> 137

```
tacttcagat acactagtaa agcctgctgt attccaacta atgaggacag atatgtaata 60
tatatacatg tatatacgta tgtatgtata tatactatat atataattat actttaagtt 120
cctaagggtac atgtgcagaa tgtgcagggt tgttaaatag gtatacatgt gccatggtgg 180
tatgctgcac ccatcaaccc atcatctaca ttaggtatatt ctccaatgc tatccctccc 240
ctagccaccc acccccagac aggccccgct gtgtgatgtt cccctccctg tgtccatgtg 300
ttctcattgt tcaactccca cttatgagtg acaacatgcr gtgtttgggt ttctgttcc 360
gtgttagytt gcwgagaatg atggtttcca kcttcatcca tgwccctgca aaggrcatga 420
actmattctt ttttatgggt gcatagtatt ccatgggtgk tatgtgccac gttttcttta 480
tccagtctat cattgatggg catttgggtt gggtccaagt ctttgcattt gtaaatagtg 540
ctgcaataaa catacacatg tctttatagt agaatgcaca tgtctttata gtagaatgat 600
ttatantcct ttgggtatat aaccagtaat gggattgctg ggtcaanggg cattctgggt 660
caagatcctc naggattcac cacantgtgt tccacataat ttaagctatt ttacactccc 720
accagcagtg                                     730
```

<210> 138

<211> 524

<212> DNA

<213> Homo sapiens

<400> 138

```
ggcagaggag gccactgtgc ctgggtcaaga aatggaactc ttacacactg ctgggtgggaa 60
tgtgaaatgg taagccactt cggaaaacag tttgacaatt tcttatgcta aaaatacacc 120
tatcagatra tttagccact tctaggtatt tacttaagaa aaaataaggg atacatccat 180
atgaaractt gtaataaaat gttctcatta tttttatttg aaatagctma aactggaaac 240
aacccaaata tccatcagca agtgaatggr taaacaaatt gtratatattg tatgcaatat 300
aacaccactc agtaatatga aaatgaacta ctgatgtttg caaacggttg aaattcaaaa 360
taattatgct gagtgacaga atccagacca caaataatac ataatgtwtt attctatttta 420
cataaagttt tagaaaaatc caaactaatc ttartttacc aaagccatac caatgggtata 480
tggggccttg ggcagkttaa acsgattatt gaaaaaaaaa attt 524
```

<210> 139

<211> 869

<212> DNA

<213> Homo sapiens

<400> 139

```
ctgattcctc ctcacatatg aaaagtgaag gttgtgagtt gttttcctct tatttaaaca 60
ttggcctatt ataactctgtg ttgggtatatt ttctcctgta agcatcctga tttttctgta 120
ggaacttttc tttaaatgac acacattgcc acttgtgtag atatttttaa gttctttggc 180
taagtccctc cctaactgcc tgcctctggt ttagggccct ccctctccac tagtggtgaa 240
tgcatgtgtc tgtctgatca gcatcactgc acacggagggt ctagtgagcc tcttgctaag 300
tgtcacacac actcttccca aagacgtgat gagttaaagt tgtattctga aatcatgaag 360
ccagagcctg tgccagacct tctgctacct ctcatagaat tgctctgtaa ttctaaattt 420
aaaattagaa gtagagagag ataagccatc gcccttttgc ctctgagaat tggctgctgt 480
ttctaataata attattttct aagatagcca gatagttaga aaaagatttt cattgatgac 540
atatctttta actttcttgc atcagtattc taaattgagc aaactgaaag attttcatca 600
```

79

```

ggaaaggagc actgtgggaa gagcccagta ttcacatttt ttccccattt ttcagaagcg 660
acatttcata tataggtgcc aaaagtgaat cggggtgcgg agagtgggaa ccttttgaat 720
ttatgattgt cacagagatg gtagaaatta tgatctgact ggaaaacaat cctgtatccc 780
ctcccaaaga atcatgggct ttttttttga attaaaaagc agacaaatag actttctcgg 840
gaaaaaaaaa aaaaaaaaaa cgcggccgc 869

```

<210> 140

<211> 586

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (439)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (563)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (577)

<223> n equals a,t,g, or c

<400> 140

```

ggggnaccag cgcggtgcg cagacgaaag gcgctctttg ccagctgaaa gttcccacgg 60
aaaaactacc atctcccctg cccaccatgg cagacgaaat tgatttcact actggagatg 120
ccggggcttc cagcacttac cctatgcagt gctcggcctt gcgcaaaaac ggcttcgtgg 180
tgctcaaagg acgaccatgc aaaatagtgg agatgtcaac ttccaaaact ggaaagcatg 240
gtcatgccaa ggttcacctt gttggaattg atattttcac gggcaaaaaa tatgaagata 300
tttgtccttc tactcacaac atggatgttc caaatattaa gagaaatgat tatcaactga 360
tatgcattca agatggttac ctttcctgc tgacagaaac tggatgaagt cgtgaggatc 420
ttaaactgcc agaaggtgna actaggcaaa ggaaatagag ggaaaataca atgcagggtg 480
aagatgtaca ggtgtctgtg catgtgtgca atgagtggaa gaatatggct gtagccataa 540
aaaccctgtc aaataaaaac ggnaacattc aggccangga ccactg 586

```

<210> 141

<211> 614

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (546)

<223> n equals a,t,g, or c

<400> 141

```

aaataaaaaag gcagtggccc caccacattt ttttcagcat agtagctggc attttggtat 60
cattagccag agtagcttca gcatataagt tattgatgtt ttccaacttc aaaagtgcac 120
tttatcctcc cagtaaattt gataatgatt tgtcacagct ttgtcatctt ttgacttttg 180
cttatggggc tcacttcgta caactataac atgaaaaagg attgtcctaa agtaaggga 240
tcagttaatg gtaggatgaa gaaactgtaa aaactcctag aaaaaaaacc tgtgtgcatt 300
tttctggaaa gttttcaaac tgtgtaattc agttttcatt caattatata atttggttat 360
atgcttttaa aaacatttgt ctaaagtgtc ccggttttct tctggtctta gagtcagctg 420
agtgtctggc atgcagccac tcgtattttt gcatccagaa aggagtaact ccctttatat 480
gaagrttttt tttttaagct tagatgctat gtaaggagaa aactatttgt aatcacatag 540
taccnngggr ggggagtgrr ggatgctttt ttaaaaaagg rtatttaagt atattatgta 600
atttaaatat aaat 614

```

<210> 142

<211> 574

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (522)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (574)

<223> n equals a,t,g, or c

<400> 142

```

ntgttaagtt ctgacattng gagaaaatac attacaaaga acaggagctg gtttttggtt 60
ttccttgttg ctgtgttttt gaattgaagg gatgtgggat ggtggtgaca gaagtctgag 120
catagtttct gaataattgg aggggagatg ggcattcttt gggactatgt ccgcattaca 180
ttgagttttc tccctctagg aagagagagt ttgtgtttta ttttctgtaa gtaaaagcta 240
catgttttag atttttaaac catattaatt gttatatatt gtatttcata attatattat 300
gtgttagtgt gtactggaat aacatgtttt atttggttag ttggtgcaa agttttctaa 360
atctactgct gtattagaaa ctgaaaaggg agggaaattc cagatgtttg atgggaacat 420
cactggtgaa tatctaggrr tggtaaagtag acycaagggt gaagragtaa ggtgggggta 480
acccttaata ttaccttkgg tatatgcccg ttttttagcac cngaatacag ggggtccttt 540
gttccccaac cttaacagca gcccctgtct ggtn 574

```

81

<210> 143
 <211> 2012
 <212> DNA
 <213> Homo sapiens

<400> 143
 tatgcaagct cgaaattaac cctcactaaa gggaacaaaa gctggagctc caccgcggtg 60
 gcgggccgctc tagaactagt ggatcccccg ggctgcagga attcggcacg agtgtagagc 120
 tcaaagaaat ctgccaacat gtatgtggac tcttgagagg tgggctttcc cagtacatgc 180
 taaacagact tgttatgcca agaggaagtg aatagaaatg atagcatcaa atatccaaac 240
 tgacaggaag tttcttttgc atagcataga acatggttgt cttctgagtt ccactaatgt 300
 tccaggatat cttggccctc tgccctctggc tgctccctgg tgtttggcac catagcgttg 360
 tcacttacaa ccattgcctt gggacacaca gagtgaactg tttgagtgat aagtaattta 420
 ggtagaaact ttacccttaa tttcaaatga taccaaacag ctcttacta cccaaggga 480
 cgctctccgt agcttctgga ttccccagtt tcttcttaga aacaaggact ccaatagcac 540
 tataacccta aacaggccct aaccagaag aatacaccac aaaatgcgat tgattttctc 600
 aaaatatcac agtcttagac actatacaaa taattcaaga aaattctttc taccctgcag 660
 tggatatagt attctattat attctccagc aaaactttta ggacttttca aactcatttc 720
 taagccaaat agtttagata aatatttacc cttatatttg gggggaattc aggtcacca 780
 tttgccgagg caagcccatc aacagtctag aggcataatc tgtgtcattc cttcccgctc 840
 ccttcataga atactacttt ttctttttgt ctctggcca ttctccatca tctgctgatt 900
 attgctaacc acaggatgct ggcaaagctt acagtgatag gcacatgtgt tcagtgatgt 960
 ccaatacact cttatcacag tggttattgc ttcttactct tttcaaatgc attattctac 1020
 cctcaacct atatccaatc attagaacta tacctgactg gagcccagaa cttgggacca 1080
 atacttaatt caaatagcag gggcttgctc acaaacatta agcccaaaaa gaagcacagc 1140
 actttgaaaa gtcaaataag cctttggtag ctctgtacat ttgcaatttt acattttgtta 1200
 ttagttttata gcactaataa cacttcagtc gtgaatctac agtctcaata tgataagtct 1260
 tagaacatgt tctagaaata gtggtacctt gctgctatta tacttagtaa cttatacccc 1320
 aatataataa taagtattaa atacagattg tgtatgcatt ctttgtgtgt atatgccaac 1380
 tgtactactt aacctcactg atgagcaatt agaaaaatac acaaattgtc atagtgaaaa 1440
 taagtcttgg tcaattcaga tgatacgtga acctgataaa tgctctaata gatatgctat 1500
 tttgtcctgt attgcttgtt ttacagtatg gtgcatgttg tttgctaagt aaaatgataa 1560
 taataataaa gtataccaat ttttaagggt gaattaaaaa tttgcacata tgcttcttga 1620
 tattctgaaa tgtattctgt ggcttaatta tcttattcat acacatttca ctttggcttt 1680
 ttacccttag gaaataactg tccaagtata tatctcgtct tctttcttgt aactttgatt 1740
 aaactgctta cttcaactta caacattgta aagccagaat acctcatttt aacagtgaaa 1800
 aaaaatatga tgacctgatg tgttctcttg tatttgattt gaactaccta aataggctta 1860
 actgtaataa taaatataca attttggcag gcattttttc ctttgttttg atgaacattt 1920
 tgttatttgt ccacttctaa ttttgtctta aagagttata aactcagtgt caataaaaaca 1980
 tcttgttata taaaaaaaaa aaaaaaaaaa aa 2012

<210> 144
 <211> 558
 <212> DNA
 <213> Homo sapiens

<400> 144
 aagttttttc ttaccccatc ctagtgagtt tgaaagtggg cctgaccaga atgtctcttt 60
 cccatttttg cccgtttgaa ttaaataataa tgtctactct ttaaaggctg aaggggtggg 120
 tgaggggatt gtttctcatt ttgtctccca agtcattttt ctgctgtgaa atatgaccag 180

```

gcttgtagga agactcatct tggagaaaat gtgaagtaat caaattgctt gagattagtc 240
tcctattgta tattagagcc aaaacacatr ataactttgg caacagggag ttgtctagac 300
tcaattttca gaggtcccat tgtagtgagt taatattgct aatcatgtca atcacttgac 360
akggaagtca gtggcaaadc tttaaagtat gcatttgata ctggcaaata tatactactg 420
atgtttcaca aaagaatcct agaatctgta gaaaacatta attacttcca tgaattattt 480
ctaaagtata actttaaagt tttgattttt ctatttaaata aaaaagcyat kgatgkgttt 540
agcakgtccc caaataga 558

```

<210> 145

<211> 1026

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (182)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1007)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1014)

<223> n equals a,t,g, or c

<400> 145

```

gcatttatat cctgttaagc attaatagct aatcactggg acttgaattc tgatggcaga 60
tagtctcttg cttagtgaga tggagttaac tatttttttag taggaagtga gaacagctga 120
ttttcatgcc acgtttcata gccccacttt tggtagacta ccaccacgct kcttcgcgta 180
anagtyggca tcttggggaat gaatgccagc ccgctcgtgg gttgggtgcaa agaagtataa 240
acatatatca ctaaggaaaa agaaagtttg tcttgccctt ctgacacagt gtgtgcaatt 300
caggcaattt ttggaaaata taaaaaattc caawttctgc ctttcagcag catcaattgc 360
taggaacatt tcattcattt ccctgtaata ttaatgttct ttaagcataa tctaataa 420
taagttgtat cctatttttt tccagcttaa tttctgtggg ttattgaaaa ccaagtataa 480
atgtgactaa aagcattttg ctttggtttt atagttaact ttcytaagggt tatggacatt 540
twataatgta acatttgatt ggcctggcct cttgacaatt cccttctagt tatgcatatc 600
ctccctgttg cccacatttc ttgttttaaa actcagtttc ttgttttcca gttgttgcta 660
tgtataaacac ccatcttgaa agagagtata taggaagtta ttcagataac tttttagta 720
gtgatattca actatagcag taccttaact catgatgagc ttaggaacat aaaagataat 780
tgttgcttga atagcacccc cagagatact gacctaatgg gtctgggggtg gagatctggc 840
atggtagttt ttttcaagct ccaatcatcg gccagacagt tgctttatgt aggttttttaa 900
atgccaaaagg cagatatgaa gtagatttaa ttaagacttg acttcagcaa tacaggggaa 960
cttaaaaatac ttrtttttct ttaaactgca ggagtcactg ttaggtnttg cttnaaaaaa 1020
ttgcat 1026

```

<210> 146

<211> 521

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (440)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (474)

<223> n equals a,t,g, or c

<400> 146

```

gggacctggc aagcggcggc tgcagggcag gtccaggggc cacatggctg aggggggacgc 60
acggagcgcac cagaggcaca atgaggaaat tgaagcaatg gcacccattt atggcgagga 120
gtggtgtgtc attgatgact gtgccaaaat attttgtatt agaattascg acgatwtwga 180
tgaccccmma tggacacttt gcttgcasgt gatgctgccs aatgaatacc cagggtacagc 240
tccacctatc taccagttga atgctccttg gcttaaaggc caagaacgtg cggatttatc 300
aaatagcctt gaggaaatat atattcagaa tatcgggtgaa agtattcttt acctgtgggt 360
ggaggaaaat aagagatggt cttattacaa aaatctccag gtgacagAAC caggcccaga 420
tgttaaagga ggaaaactgn aggaggaaga tggttggaatg tggaagggtg atnccattt 480
ttagcatggt cagccgggaa agttcgggtt aaaagcattg g 521

```

<210> 147

<211> 557

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (17)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (527)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (543)

<223> n equals a,t,g, or c

<400> 147

```

ggattaacca ttaaatngat tgaaaaggaa actttgcacg gtatgagctt cataccccca 60
ccaaacaaag tcttgaagggt atttatttta ccaagtatat ttttaaagtt gttttataag 120
agagactttg tagaagtgcc tagattttgc cagacttcat ccagcttgac aagattgaga 180
ggcccatgcc aacagtctaa tctaagagat tagtctttca aactcaccat ccagttgcct 240
gttacagaat aactcttctt aactaaaaac ctagtcaaac aaggaagctg taggtgagga 300
gatctgtata atattcctaat ttaagtaagt ttgagtttag tcaactgcaa tttgactgtg 360
actttaatct aaattactat gtaaacaaaa agtagatagt ttcacttttt aaaaaatcca 420

```

84

```

ttactgtttt gcatttcaaa agttggatta aaggggttgta actgactaca gcatggaaaa 480
aaatrgttct ttttaattctt tcacctttta agcatatttt atgtctncaa aagtattaaa 540
aancttttaa tacaagt 557

```

```

<210> 148
<211> 1023
<212> DNA
<213> Homo sapiens

```

```

<400> 148
ggcacgagga accacettct gtaggacagt caccaggcca gatccagaag gcttgaggcc 60
ctgtgggtccc catccttggg agaagtcagc tccagcacca tgaagggcat cctcgttgct 120
ggtatcactg cagtgttgt tgcagctgta gaatctctga gctgcgtgca gtgtaattca 180
tgggaaaaaat cctgtgtcaa cagcattgcc tctgaatgtc cctcacatgc caacaccagc 240
tgtatcagct cctcagccag ctctctctta gagacaccag tcagattata ccagaatatg 300
ttctgtctcag cggagaactg cagtgaggag acacacatta cagccttcac tgtccacgtg 360
tctgtctgaag aacactttca ttttgtaagc cagtgtctgcc aaggaaagga atgcagcaac 420
accagcgatg ccttggaccc tccctgaag aacgtgtcca gcaacgcaga gtgccctgct 480
tgttatgaat ctaatggaac ttctgtcat gggaagccct ggaaatgcta tgaagaagaa 540
cagtgtgtct ttctagtgtc agaacttaag aatgacattg agtctaagag tctcgtgctg 600
aaaggctgtt ccaacgtcag taacgccacc tgtcagttcc tgtctggtga aaacaagact 660
cttggaggag tcatctttcg aaagtttgag tgtgcaaagt taaacagctt aacccccacg 720
tctgcaccaa ccacttccca caacgtgggc tccaaagctt cctctacct cttggccctt 780
gccagcctcc ttcttcgggg actgtgtccc tgaggtcctg gggctgcaact ttgccagca 840
ccccatttct gcttctctga ggtccagagc atccctgctg gtgtgtgacac cctctttccc 900
tgtctgtccc cgtttaactg cccagtaagt gggagtcaca ggtctccagg caatgccgac 960
agctgccttg ttcttcatta ttaaagcact ggttcattca ctgaaaaaaaa aaaaaaaaaa 1020
aaa 1023

```

```

<210> 149
<211> 1256
<212> DNA
<213> Homo sapiens

```

```

<400> 149
gctcagcctc ccaaagtgt ggtattacag atgtgagcca ccgcaccag cctgagtttc 60
tctttctctc tttttaactt tattttttga aaaaccgggt agactttgtg gggagcattt 120
ttgttgataa ttactgate taaagctgag tgatttttta aaagaatttg aatctaatag 180
atctgtgggt gaatttsctg tgttgttatg aagtcacccc tgtgggcaca ataacataac 240
tgttggtagg agttgtttga gctattctgg agattatttg gtaaagtata ctaaaagcct 300
taaaaccatg tatgtgcgt gtttgaacca gtaagccact tctttgacat tagaagacat 360
tagaagaaat aatcagcctt gcataaaact tatggatgaa agtattcatc acaatattat 420
ttataataaa aaattgcaaa tgttataaat gaacaatttg gaaatgggta aagaagtgat 480
ggtgcattgt gtggtagaat attatgcata tgtttaaaga atcatatttt ctaagattat 540
ttggaagcat gtttggtaat gtcaagtggg gtaccccaga tacatttttag acatttatcg 600
tcatcatctg ctctgagtgg aaggccgttc agagaggcta gaggttctta ttctggctat 660
aaattatgtg agtaaaattg tgctaaccag ttaaaagtac tgtacacca tgctcaatat 720
atagtcctgg aaatagcaat tgaaacatgt cttctcacia gagaaaatga cagttttaat 780
gatgtatttg atgaatttaa actttaagtc aggtgtgtgca aattggaaag aagacttgtg 840
gtgttttaag ttgctgtgga cacttttaag aaacttagaa cccatggaac ccttgtttat 900
cgccatgcaa attacaatct tgaatgagtg ttttttaaaa ataaagtatt agaaaaatgt 960

```

85

```

gtagttaaaga tgtaaaatta aaaaatggaa ttctccatta actgtggatt ttactaaata 1020
gaattactgg tgaagcagat ttatccatcg agactatctg gtatgcgta tgtagtagt 1080
ctgttgctgc tgaaagatgt ctgtgtgcct gtatcaacat gtgacttcat gtaaagtttc 1140
tttgtgttca cagttcttag caaatgcagt tacaatccat agatagccag cagtggatgt 1200
tactccagga aaatgcagga ttaaaattgt ccttgtgtaa aaaaaaaaaa aaaaaa 1256

```

```

<210> 150
<211> 698
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (683)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (692)
<223> n equals a,t,g, or c

```

```

<400> 150
cctcgctcaa gccctcagag aagaacattt tcacctctt catggtggcc acagctgcca 60
tctgcatect gctcaacytc gtggagytca tctacctggy ragcaagaga tgccacgagt 120
gccctggcagc aaggaaagct caagccatgt gcacaggta tcacccccac ggtaccacct 180
cttctctgcaa acaagacgac ctcttttcgg gtgacctcat ctttctgggc tcagacagtc 240
atcctcctct cttaccagac cgcccccgag accatgtgaa gaaaaccatc ttgtgagggg 300
ctgcctggac tgggtctggca ggttgggcct ggatggggag gctctagcat ctctcatagg 360
tgcaacctga gagtggggga gctaagccat gaggtagggg caggcaagag agaggattca 420
gacgctcttg gagccagttc ctagtcttca actccagcca cctgccccag ctcgacggca 480
ctggggccagt tccccctctg ctctgcagct cggtttcctt ttctagaatg gaaatagtga 540
ggccaatgcc cagggttgga gggaggaggg cgttcataga agaacacaca tgcgggcacc 600
ttcatcgtgt gtggcccact gtcagaactt aataaaagtc aactcatttg ctggwaaaaa 660
aaaaaaaaaa aaaaaaaaaa ccnggggggg gnccggta 698

```

```

<210> 151
<211> 1710
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (142)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (208)
<223> n equals a,t,g, or c

```

```

<220>

```

<221> misc feature
 <222> (242)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (317)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1644)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1707)
 <223> n equals a,t,g, or c

<400> 151
 aatttcggcc cgagggtgag ggcagctgga gtgcgttctg ccgaagcttg tggttgcacg 60
 cccttcgtct taggggctac ctcccggttg gagtgtgtgc ggtggtgcac ttgggggttgc 120
 ttctcgctgc gtggccgcac gnggctgaac ctttcccact ccataccctc cccgcacccg 180
 gaccagcccc tgggacgccc tcggacgncc acccgctcca accctgggga agcctcagag 240
 tngcagcgaa ggccctyttgc ctttccgcct ctgcgcttgc tgtcatcgcc cacgtgcttt 300
 gttgttggtc ggtgcanacc atgtccaagt ctctgaagaa gttgggtggag gagagccggg 360
 agaagaacca gcccgagggtg gacatgagtg accggggcat ctccaacatg ctggatgtca 420
 acggcctctt taccttatcc catatcacac aactggctct cagccataac aagctaacaa 480
 tgggtgccacc gaacatcgca gaactgaaga atttggagggt gctcaacttt ttttaataacc 540
 aaatcgagga gctgcccaca cagatcagta gccttcagaa actcaaacac ctgaaccttg 600
 gcatgaacag gctgaacact ttgccacgag gcttcggctc cctgccagct cttgagggttc 660
 tggacttgac ktacaacaac ttgagcgaaa attctcttcc tggaaacttc ttctacctga 720
 ccaccctgcg tgcactctat ctaagtgaac acgattttga aatcctgccg ccagatatattg 780
 ggaagctcac aaagtgtgag atactcagcc ttagggataa cgacctgatc tcgctgccta 840
 aggaaatcgg ggagcttacc cagcttaaag agctccacat tcaggggaac cgcctcaccg 900
 ttctgcccccc agaactagga aacttggatt taactggcca gaagcaggta ttcaaagcag 960
 agaacaatcc ctgggtgacc cccattgcag accagttcca gcttggcgtg tcccatgttt 1020
 ttgagtatat ccgttctgag acatacaaat acctctacgg cagacacatg caggccaacc 1080
 cagaaccacc gaagaagaat aatgacaaat cgaaaaagat cagccggaaa cccctggcag 1140
 ccaagaacag ataaggaagg gattggcatc ggctggcctt ccagcacctt ctctctccaa 1200
 cacttcattc tctcttgccc tgtctctcaa ataaacccaa tgcctgcgtgt gaggcctttt 1260
 ttatttttct tttcactctc tttctaattg tttccacctt accttttaga ttcttttgc 1320
 aggtggggaga ttgttataag gtcttttaaac catttccatt tgtttcttta acattaccaa 1380
 aagcagggaa caaagctctt attcaactgc gaattccata gtgggctctg gcttttcttg 1440
 aatagatatc acaagggttg ttattatcaa aagaataatt aaaatcatgt aaccatttaa 1500
 atgtcactgt taacactttt cactctttct gttgattcac ctaactcatt attttgcttt 1560
 attaaaagtc ttccctcacc accgagatat gctaatttaa cttacaaatg attttaataa 1620
 aatcttgagt ttgtaaaaaa aanaaaaaaa aactcgagag tacttctaga acggccgcgg 1680
 ggccatcgat tttccaaccg ggtgggnacc 1710

<210> 152

<211> 1121
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (532)
 <223> n equals a,t,g, or c

<400> 152
 ggcacgagggc agaatgggtcc tgccagccac agcagggccc tgggtggggat ttgcactggg 60
 cactccaatc ctggagagga tgccagggac ggggatgctg aggaagtcag agagcttggg 120
 acggttgaag aaaactgagt cttgggcaat ttgtgctaaa actaggtgag ttgccaaacc 180
 caaggcatct taccaacagc tggtttgggg gctggtttcc ctgggtgtgt gtgttaccta 240
 ccctttggct tggcttgacc tctccttggt agtcacctg agccctccca gggccagggt 300
 cctgacagtg ttggtttttg cacatccact ggaaagggtg cattaatgac ccagtgttag 360
 aatgcaagag gtcagggttat tctagccctc atggctgaag gccagtcct ggctccacca 420
 ctctccagc cagaggggtc ggaccatcca gtgctgtcc tcgccacagg gcctccaggg 480
 agcattcggg tcaawtccat ggacaccctg ggctacaaac caaggctgct gntcatccca 540
 catcgtgtgg ggcagtgtcc atcccctgca gctacttggg gacttaacaa ctycaggagc 600
 cctgtcagct gccctcctcc acctaaacct ctctgactct tctgctttga caaagaaaat 660
 gacattgggg aggggaggtg ctccgcctcc cagcttttct caaaatagtc ctatagatac 720
 tggtaatctg gaaatgaaga agtaattctg tctctgcacc tacttttgca gaatgttcaa 780
 ggaagtattc tgtgttagta ttaatgcaa aaagtgtgtt ttaaagggtt tgtactcagc 840
 acatcataca aaccacatta ctctgtcac ttccaggcat cgggactggc tggcgccctt 900
 gttatgtgct attttaatca gtgtaacatt ggtcaagttg ttacccatgt atgctgtgtt 960
 tatcatgtgt atatcgtcya gaaagtatta aggctttagg tagatgcaac tggcgaacct 1020
 tggagaggga atgctgattg tcttgaccaa acccacagcc tgtctcttct cttgttttagt 1080
 tacttacggc aataaatcat ctatgagtta gtgcaccgtg a 1121

<210> 153
 <211> 445
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (440)
 <223> n equals a,t,g, or c

<400> 153
 ttttcttgca tctgcccgcg atctttctcc agacctttct gcgagtacga gccaaaccggc 60
 agacccgact gaatgctcgg attgggaaaa tgaaacggag gaagcaagat gaagggcaga 120
 gggaaggctc ctgcatggct gaggatgatg ctgtggacat cgagcatgag aacaacaacc 180
 gctttgagga gtatgagtgg tgtggacaga agcggatacg ggccaccact ctctgggaag 240
 gtggyttccg aggctctggc ttcatcatgt gcagcggcaa agagaacctg gacagtgatg 300
 ctgacttgga tgtggatggg gatgacactc tggagtatgg ggaagccaca atacacagag 360
 gctgatgttc atcccctgca caggcgagga gctggttgaa gccaaaggaga gagaggcatt 420
 tcggggcgca ttcttaaata gccgg 445

<210> 154

88

<211> 798
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (638)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (665)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (698)
 <223> n equals a,t,g, or c

<400> 154
 agctcttaga caggtacaga gaactacaac ttagtacaga aagcaaagta acagaatttc 60
 tccatcaaag taaattaaaa tcttttgaaa gtgagcgtgt tcaacttctg caagaggaaa 120
 cagcaagaaa tctcacacag tgtcaattgg aatgtgaaaa atatcagaaa aaattggagg 180
 ttttaaccaa agaattttat rgtctccaag cctcttctga aaaacgcatt actgaacttc 240
 aagcacagaa ctacagagcat caagcaaggc tagacattta tgagaaactg gaaaaagagc 300
 ttgatgaaat aataatgcaa actgcagaaa ttgaaaatga agatgagggt gaaagggttc 360
 ttttttctta cggctatggg gctaattgtt ccacaacagc caaaagacga ctaaagcaaa 420
 gtgttcactt ggcaagaaga gtgcttcaat tagaaaaaca aaactcgtg attttaaaaag 480
 atctggaaca tcgaaaggac caagtaacac agctttcacm agagcttgac agagccaatt 540
 cgctattaaa ccagactcaa cagccttaca ggtatctcat tgaatcagtg cgtcagagag 600
 attctaagat tgattcactg acggaatcta ttgcacanct tggagaaagg atgtcagcaa 660
 cttanaataa agaaaagtca gctttactac agacggangg aatcaaaatg gcattaggat 720
 ttaggaccaa cttctaaatc atccgtgaag gaaatttggc aagcaaatga aaaccagatt 780
 cctcggttaa gatgcatt 798

<210> 155
 <211> 400
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (74)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (379)
 <223> n equals a,t,g, or c

<220>

89

<221> misc feature
 <222> (383)
 <223> n equals a,t,g, or c

<400> 155
 ggaatctgga agcctgactt tgcccccagg gaagttgggg accgccttcc ctcccttctc 60
 cacctctcac tctnggcacc ctctccaatt gcactaaagt agctgttggtg ccagtctgcc 120
 cccacaagg ggggaggtct ctgcttycag tcttcttccc ccgctgcctc cgctmccacc 180
 ctggacaatc tccttgtttc ccttggtgtc mtggayagct cagctttgta tgtgtgtttg 240
 ggggggtgggg gtgggttctg gcttgagtgg gtttggcagg ggtttgggaa gggttagggg 300
 aggatggagg atgaagtctc ctacccctt ctccagctcc aggccacaga agcctgggaa 360
 agggagggtg cctactctng gtngctagtg tgtctttgca 400

<210> 156
 <211> 1757
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (596)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (647)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (648)
 <223> n equals a,t,g, or c

<400> 156
 gccagccacc attttatctc tctaaagtct ggtcccagta ttaaacctat tctttagtaa 60
 actcatatta ctgttctaaa ttgaagaaat tatttattac tctgtacttc tagactcaaa 120
 attctttatc aaagatagtc tcaaagaggt agtacaagtc ctgtttaact gcactttttc 180
 acattcacag tgcttcctct gatattcttc cttacatcat tatacactgt tgatatcatt 240
 ttactcttct ttctcttcta catttcttaa attttgggtc ttttctgtga catgtgtttt 300
 agcggggccc ttttctttga actttgtcta attagcctgt acatttttgt ttcttttaag 360
 gtagaacaga tctttttttg tttctccttt taagtctact ggtttttaaa gaggtaaatg 420
 tatccataga ccacagtgcc ttgctttttc ctctgccagc acatggagca cgggattaga 480
 tgcacaaacc tatttaggga actatttttg tagatgtttg agtttataca gaaattgcag 540
 ctggtatttt attttgctgt acatttactc aacttgtcca ttagtattta actatntcca 600
 gagtttggtt aggagtaaga attgacccat tcgttagttt accatanntt ttcttggtat 660
 aaaaaggagc cagaaataag ccttattgct aaataattaa ttatgtaagc ccacctaggt 720
 cctgcataag atccccctca catacttcac aatataatg tgtgtgtgtg tgtgtgtgtg 780
 tgtgtgtgtg tgtgtgtgtg tgtgtatktg gctaaaaaat tatactgcca aaattactga 840
 ttataaatac ttgactacac tgattgatgg gacaaaatga ttaaagtatt ttcagggatc 900
 ttattccata tgtcaccacc aaagatttct acagtgttat aaagtatata aatattccaa 960
 atttctgtgg ttaaataattt ttttcttttt tttccttttt tagaataaca cagtctgtgc 1020

90

```

tttccaaaaa tgcttgaact tttatgttgt taagaaatat ataatgatat cttacattaa 1080
gcatgagtcct aatttgtatt aattgggatg gactaaattt tcatttgatt atcaggaaaa 1140
ttaaggagtt atatatattaa aagcaatttt ctgtgttttc ttctttgtaa gttgactcat 1200
ttgtgaagca attaggcaaa ttttgagaag atcattgtta ttgtggtttg cagtatatat 1260
ttcttagtaa atatcactta agattaaatt tttcagaaag aaaattatag cttttttccc 1320
aaaatatatt taagatttaa tctttttgta gtatgctaca gatttaatta tattaactct 1380
tttttaagac attgaccatg acttaacatt ttgccttcta acacctttta aatctatgta 1440
ctttaatagt taagagaaaa taagtttgca gatttttaat aatctgtttg taaaaggcta 1500
tctctaagcc tagtatgtgg gtaattttac aggtgtgttt ttgataact ttaatatata 1560
ataaactcat tttatttgtg gcaattcgcg tttctttttt tatgccagag tacatatgtt 1620
ggattccatg aattgggtatt acttattatt atgtgttgat taaatatatg cacacactta 1680
ggattacaga tcacagagca aattatgaaa atcataaaca ttctggtatg gtcattccata 1740
ggattatgaa aaagaaa                                     1757

```

<210> 157

<211> 1245

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1245)

<223> n equals a,t,g, or c

<400> 157

```

gaaagccctg aatgttgtac aaagtgtttt gcaaatacaac ttaagcaatt ctacaaacag 60
aggatcagta gctgctaaga aatttaagga catcatacat tatgatccaa cgaagcaaga 120
ccatgccact tacgaaagaa aaagagatga taagccaaaa gaaagtaaag caaaacgaaa 180
aaagaaaagg gaggaagctg agaaactacc tgaggtgtct aaagaaatgt attataatat 240
tgctatggat ctgaaagaaa tattccaaac tacaaaatat accagtgaaa aggaagaggg 300
cacaccctgg aatgaggact gtggtaaaga gaaacctgag gaaatccagg accctgcagc 360
tctgaccagt gacgctgagc agcccagcgg gttcacgttc tctttttttg attcagacac 420
taaagacata aaggaagaga cctacagagt tgaaacagtg aaacctggaa agattgtctg 480
gcaggaagac cctcgtttac aagacagcag ttcagaagar gaagatgtta ctgaagaaac 540
agatcacaga aactccagtc ctggagaagc atcattactt gagaaagaga ccactagatt 600
tttctttttc tctaagaatg atgaacgact tcaaggttct gacttattct ggagaggagt 660
aggaagtaat atgagcagga actcttgagg ggccagaaca accaacctgc gtatggattg 720
tcgaaagaaa cataaagacg caaaaaggaa aatgaaacca aaataataaa tgtcagctgg 780
ttttgatact gaatgtgaac aaggctcacc taaggaaact gaccagaaa acagttttag 840
ctgacaaaaga agaaatttca gagtgaagga attttaaaaa tctggctgac ggaatatcat 900
tctggttgcc atctttttct gtggaactcc tctgcatttc ttctaagta attacttcaa 960
aaattaaatt caacttctta taaaggaaga acaagatagt ccttgaaaat actttttgta 1020
tataatctct ttgccctcta tcttgagtaa ctaatggaca tcttctcatg caaggtttay 1080
atgaagcctt tttwaataaa tgagtcaaag cacttgattt ttccagccta ggctttgtgt 1140
gaattatagg ctatttgaaa ttttatttct gattatgtca aatacacctt ccgattttgt 1200
catttttgtt taaactgata aattacaagt caacattgag ttttn                                     1245

```

<210> 158

<211> 379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (375)

<223> n equals a,t,g, or c

<400> 158

```
gtgagctgag accatgccac tgtactccag cctgggcaat agagcgagat tctgtctccc 60
aaaaaaaaaca aaaaacaaca acaaaacttg ctaccaccca gggattttct gctattttaa 120
agggtgaattt cttttctggt actaaactgt agctgcttaa cttagtaaag gctgtgtttg 180
gccaggcctg tgccagaggt cacctggagt gctccaccca ctggcaggca agtcctattc 240
ctattcaccc aggatcccca aggctgggct gggatataaa tgttgggata ggaaagaaat 300
atttcctttt tagaggaaaag caagaagaaa cattgcctga aagtgattty ctagtcattt 360
ccattagtac agaangtta                                     379
```

<210> 159

<211> 474

<212> DNA

<213> Homo sapiens

<400> 159

```
ctttatcata ttttacaat gtgtgagtct gctatggatt agaaattaat aagagatttk 60
gccacagata gtttgagaag ccagcactg ccaactcaaca aatgctggtg cattcagatg 120
gtgaaatatt ctgcagctat taaaggagtt aaaactgcct ccacttacct ggaggcccat 180
ctgtgacacc tttttagggt aaaaggaaaa gaaaaacttg cttaggactg aatatgagcg 240
gttgcaattt gtaacaatga tgtatatata catatacatt ttcattgtatt tgtatgaaca 300
taaaagtatt gaaggatatt catcaaactg ctaaaagggt tgcttcagag taacggactc 360
ggagaaggca gattaatttt ctcttaatgg aactctgtat tgtatcactt gtaaaaaataa 420
gcatgtgtta tctttatgat aaaaaagtaa aaacctaataa aaaaaaaaaa aaac 474
```

<210> 160

<211> 1444

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1373)

<223> n equals a,t,g, or c

<220>

<221> misc feature
 <222> (1425)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1430)
 <223> n equals a,t,g, or c

<400> 160
 gggmntagac accttagaga ttcagcagca agccctgcta agagagcagc agaagaggct 60
 gaacagaata aaaatgcagg aaggtgccaa agttgactta gatgccatcc caagtgctaa 120
 agtacgagag caaagaatgc ccagagatga cactagtgat ttcttgaaaa actcattatt 180
 ggaatctgat agtgctttta ttggggctta cgggtgagaca taccctgccca ttgaagatga 240
 cgtcctccct ccaccatcac agttgccctc tgcacgggag cgcaggagga acaaatggaa 300
 aggactagac attgatagca gtcgtcctaa tgtagcacca gatggtctct ctctaaaatc 360
 tatatccagt gttaaagtgtg atgagcttag agtgagaaat gaggaacgaa tgcgaagact 420
 gaatgaattt cacaataaac ctattaatac agatgatgag agttcactgg ttgaccctga 480
 tgacatcatg aaacacatag gggatgacgg atcaaaactct gtagcaactg agccctggct 540
 ccgcccctggc acttcagaaa cgctgaaacg tttcatggca gagcagctga accaggagca 600
 gcagcagatt cctggaaaac caggcacttt cacttggcag ggccctgtcga ctgcacatgg 660
 ttaaaataaa cctgtactgg acccagtagt gccttttaag gtgaaaggaa tggtaaactct 720
 gtacctttaa tatgtcctac ttttggcccc tacctgaaag ttactttttt tccatcatct 780
 gtatataaaa ttatttttat catgatgtat attatgtaca taaataaaaag gccatgatta 840
 ttgatttata taatagaatt gtatagatta tttttgcaca gttttgtcat aaattagggg 900
 ggtaatgaac tggattgaac tactatatgt gcattatatt gaattctgct tgtcattaag 960
 ataaggtgaa taagtgtctt aaacgtcctg taaaaccgga ctcccctttg ttacatgcac 1020
 attttccatt gttacctcga tgcaaaagaa ttcatttagt aggtacatct attgtagctg 1080
 tgattattcc agtttctgtg tgatgcaatc aaatgtccta ttaattaatt attatttcat 1140
 gtcatttcta gctactgata cagcagaaat gaagggaact gtaattactt gtatttttgt 1200
 aagccatacg ttaaagtgtt gttacatcat ctttctgctt ctatttttat gccaatgaag 1260
 gcatttgtct tgttactaat tacatgatgt aactacttct tgatataaat aaatttttat 1320
 tttaattact aaaatctttt taactactat ggagctttct agactagttt tcnagagggt 1380
 gaatagaggt ggggacaccc ggggagtcaa ggacagagga gactnggagn cttccttctt 1440
 ccca 1444

<210> 161
 <211> 449
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (268)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (269)
 <223> n equals a,t,g, or c

93

<220>
 <221> misc feature
 <222> (368)
 <223> n equals a,t,g, or c

<400> 161
 aattcggcac gagttggaat gtgagatggt ggttgagagt caggatctct tttaaaagtg 60
 atcttgagca agttatttaa acttttcta atcagtttc tttatctgta aaatggagggt 120
 aatgggaata cttacctcaa attgctgaga gaattaaatg aaataattct gcaagatagt 180
 tatcacagta aagcagtaaa tgctccattc aggggtaccat tactattgac tgccttaaaa 240
 atttaattct ctagccagggt gcgaaaannc atgcttgtaa tctcaacact tttggaggcc 300
 gaggtgagat gatcatcttg agcccagag ttcaaggatt aaccagagta acatagcagg 360
 gatcttgnct ctattttttt aaaaaagtca ccttgtaaca ctggtgaatt ggataaggag 420
 caattcagat gtagcgaatt ttaataatg 449

<210> 162
 <211> 573
 <212> DNA
 <213> Homo sapiens

<400> 162
 cccaccctga aagccctgag ctttctgcta tcaaagaggt tttaaaaaaa tcccatttaa 60
 aaaaaatccc ttacctcgggt gccttcctct ttttatttag ttccctgagt tgattcagct 120
 ctgcaagaat tgaagcagga ctaaattgtct agttgtaaca ccatgattaa ccacttcagc 180
 tgacttttct gtccgagctt tgaaaattca gtggtgttag tggttaccca gtttagctctc 240
 aagttatcag ggtattccag agtggggata tgatttaa at cagccgtgta accatggacc 300
 caaaatttac cagaccacaa aacttttcta atactctacc ctcttagaaa aaccaccacc 360
 atcaccagac aggtgcgaaa ggatgaaagt gaccatgttt tgtttacggt tttccagggt 420
 taagctgtta ctgtcttcag taagccgtga ttttcattgc tgggcttgtc tgtagatttt 480
 aggacccwat gctgcttgag rcaactcctc ttaggggtggc aaaaaggcag grtggccggg 540
 cgcgtggtca mgsctgtaat cctagcactt ggg 573

<210> 163
 <211> 1037
 <212> DNA
 <213> Homo sapiens

<400> 163
 aattcggcac gagctgtctg cgaagtggcc cttgattaca aaaagaagaa acacacctaa 60
 acactttatc tccaagttac aaaagtttga ggtgcagagg gaaggccaga tttttttttt 120
 aatgaaatta tatagattag atctcagtat ttaaactgtt cctcaatttt gtgaggctgt 180
 gttggaaaata acccgctctc agtgctgttg gtatgcaagg cagcgggtgtc taatcaatat 240
 ttctgtgtgt caccagaggc aaaatgtacc aatatcctga caccattctc tctccattta 300
 cttctggttg ttacctgac tcttgactct tagaagtgcc cgagatgggg ctaaccttta 360
 ttaaacagat cgcattattat gatcttgctg cagccacagt gcagctccac attaaactct 420
 cagaccaaac catttgatc tggcatcact tactaacaca cgacatgcgg cttttctgca 480
 tcaactgcta tgacggttaa gaatgtcagt atacaagaag gaatagaaaa ctgatactgt 540
 tttaaataat ctgtaatttc aatttttttt tttttttgct gaaatacatt atattgtacg 600
 tttgagataa ttctagtaca aggtataata aaactagatg tataataaac cctttaaatc 660
 attggttaagt gtacaagtgg tggaactgaa gcatttactg gacaaagtaa tgttactcta 720
 atggttactt gctcgtgcgt tgccacactg tggtataatt tgcttcattt ccttgctatt 780

94

```

tgatacatag tgtgcatttc tctgtcactg taactattgt aatgacaaat tttcatctta 840
ctgcacaatc aaaatgacat tgataggaat gaactccaga ggctgggcct gaacagggag 900
gtggtcgctc aggcctgggtg ctcagtcgta cgacctgtac ctctcaactt ttgccctatc 960
tgttaaatat atgctatgtc attaaatgct tttaaatcta aaaaaaaaaa aaaaaaaaaa 1020
aacggggggg ggcccgg                                     1037

```

```

<210> 164
<211> 921
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (881)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (908)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (913)
<223> n equals a,t,g, or c

```

```

<400> 164
ccccccccc ctttgtggac agctgtgtta ataaggccaa ttttctgaga atgtgggaaa 60
gattaaaata ttttaactgtt tatctttcac agagtagcag tagctctgat taagcctata 120
ggcaattaaa agtagtttgt ctgtaaaaag agggaaagaa ataagatttc ttacccatt 180
ttatggactt ttaaaaatta aaaaactgog cccccgccca ggagctcttt tcttatgaca 240
tataaattat gacattttata ttctttatat gactttatgt tctcttctta tgacatttaa 300
attcttttaag tagtttgttg gtccaataaa ctagacgttg tataatctaa attgagccct 360
tgtatatcta aaactgatga gttgtttcta aattgttgat tgtccattta cttgcctttg 420
gtattaagat aatgcaagta aagtttagta agtcattgga taatgaaatg attatgtttc 480
tgaagaccat attatatattt taatttttag aggaatcatg ccatcccca aaaaatcaag 540
aaatatttga attttaaatt ataagttcat ttgttaaaag acatttttac aaatgtctga 600
aaatctttaa atactttaca tctaccttta agtagtagaa tacagagctg taaattttcca 660
tgcctttttt cctgatatta agttttatag taaaaaagca actagtgatt gcacaaagaa 720
tataaaaatc caytcttttt acaaagggtgt gaattttaat aacgttattg attggaatat 780
gaaaataaac caatcattta agagcttttt agcaaatgat ccaattctta ctctttttct 840
ccaagatttg gaaaagcata atgtttttcc tcctaaagtt nggaatccta gaaaagcccc 900
ggtgagtngg acnaatgttc c                                     921

```

```

<210> 165
<211> 465
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature

```

<222> (428)

<223> n equals a,t,g, or c

<400> 165

```
aattcggcct cacagagatc atcatcttta ccaccttcaa atcgtaaadc aagtactcca 60
aaaaaaactt attctgagaa agccaccgat aaccatgtta atcatagctc ttgccctgaa 120
ccggtgccaa atggagttaa gaaagtatct gtgagaacag cctgggagaa gaataaatca 180
gttagctatg aacagtgtta gccggtttca gtcactccac aggggaatga ttttgaatat 240
acagcaaaaa ttcggaccct agctgaaaca gaacgatttt ttgatgaact tacaaaagaa 300
aaggaccaga ttgaggcagc actaagcagg atgccttctc ctggaggacg ratcacttta 360
cagmragggt taaatcagga agccttggaa gatcgtttgg aaggattaat cgagaactgg 420
ggttcagntc gcatgacgct aaagaattcc atgttttgcg cacct 465
```

<210> 166

<211> 752

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (651)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (662)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (684)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (693)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (700)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (711)

<223> n equals a,t,g, or c

<400> 166

```
gtggaaactt tttccatcct gttttctctg ctatatctgt cagcccccat ytcaccwac 60
atcagagaag acagcatcgt gaagcttctg tggcagcctc ctaaggaagg ggctgccaat 120
```

96

```

ctgtagttgg cagatgctat aggaattgct tacaaatgct gtctttaaga aaaatgttct 180
tatatTTTTc ctatgggcaa aatgaaggct tgggtgctca tctaaagctc agccaactcc 240
tgaagcactc tctcagagca tactgctgct gtaatgggct ggcttaatta tcggcagagt 300
gcttgaaaag gctttgcaga cctccccctgc cccaagact gggtgacttt atatgtactt 360
cattcaaggg taaatcaggg agacgttctc catttatctc ttcgtccttc ctgcctggga 420
aagtgatagc actaaatatt tcccagcagg atggggtagt gtttctcaaa ggaatcacc 480
tttcctacc ttcagactca ttctttaccc ttccattgst ccagtgtga tggaggccaa 540
agacaacccc agggttttca taggaaattc actggaattg tgcgcaattg tctttgtagt 600
ccttttgctt tttttttttt taaatattta tgttggaat agcatttggt ngggtatttt 660
gntttaaaag gcctcactct aagntattac cgncccttn attggttttt naaagacatg 720
tgggggggata tagtttttaa aaaataaacg ta 752

```

<210> 167

<211> 1631

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (255)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1620)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1630)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1631)

<223> n equals a,t,g, or c

<400> 167

```

tccagagatg tttcctgtcc tccccgggtc ccacttgctg ytcaataacc ctgccctgga 60
gttcatcaaa tacgtgtgca aggtgctgtm cctggacacc aacatcacaa accaggtgaa 120
taagctgaac cgagacctgc ttcgcctggg ggatgtcggc gagttctccg aggaggccca 180
gttccgagac ccctgcccgt cctacgtgct tctgagggtc atctgccgca gctgtaactt 240
ctgccgcgac ctggnacctg tgtaaagact ctcccttctc agaggatggg gcggctcctgc 300
ctcagtggtc ctgctccaac tgtcaggcgc cctacgactc ctctgccate gagatgacgc 360
tggtggaagt tctacagaag aagctgatgg ccttcaccct gcaggacctg gtctgcctga 420
agtgccgcgg ggtgaaggag accagcatgc ctgtgtactg cagctgcgcg ggagacttcg 480
ccctsaccat ccacacccag gtcttcatgg aacagatcgg aatattccgg aacattgccc 540
agcactacgg catgtcgtac ctccctggaga ccctggagtg gctgctgcag aagaacccac 600
agctgggcca ttagccagcc ccgggccccg ggtgcctctg cgtccgtgcc aggcctcctg 660
atgccaaggc cacatccccg tgcttccagt gaccagacca ctgaccaccc tgactgtcca 720
aacctgtgac cccaggccag ggaacgggga ggaaaccaa gaaaaccatt ttcaggggagc 780

```

```

tcagacgtca caggaggggag cgggagcagg atgtggccct ggcctcgcca gagcacctga 840
agaagcaggc cgtgagcgag gctgcgagtg ccctgggcgc cgtttctcac gcatgaatgc 900
ttttccaggc ctctgttgct tcctgcacca cacctggtgg ggtgggagcg tcctctagtg 960
cccctagttc tttgtcctgc ctcccagagg gaggaaaaag cccctggggg cttctggctc 1020
cctgagattg ggctctgaga cgagacgggt tcccaaggcc ctggtggggc tggagtctca 1080
cctgtttgca tggagaaatg ggctggcccc acagcctcac aggagcagtt tgtgggctgg 1140
tttccccrgg aatccagacc ctaacccgtg agaatctgga ttttggcttg tgagccctgc 1200
ttatttggag ccgggtctag agggaaccct ctatcagcct caggaaaaca agacctctgt 1260
gcacctcact tttggctcac tgcagccctt gtcccttcacc tccacacagg accagctgga 1320
agcagaaaga agaaaggcca atttcacagg gcaccaaaca agtatgaaat gtaaatacaga 1380
aatgcagaca ccccagacga gagcctcaca ggagggaggg ggccccacag gctccccagg 1440
aggctcgtgt ctttggccca gagccagcct tagtttgtcc ctgccatcta ctgtctgagg 1500
ccatcgctgc tacactttgt ttttatttgt atttcatact gaagtttcaa maaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaan n 1631

```

```

<210> 168
<211> 740
<212> DNA
<213> Homo sapiens

```

```

<400> 168
tttttgaatc ggttgtggcg gccgcggcga ggaatggcgg tatttgtgag aggagtcggc 60
gtttgaagag gtggaactcc tagggctttt ttgagagtgc tgatttagaa gaatacaaat 120
catggctgaa aatagtgtat taacatccac tactgggagg actagcttgg cagactcttc 180
catttttgat tctaaagtta ctgagatttc caaggaaaac ttacttattg gatctacttc 240
atatgtagaa gaagagatgc ctcagattga aacaagagtg atattgggtc aagaagctgg 300
aaaacaagaa gaacttataa aagccttaaa ggacattaaa gtgggctttg taaagatgga 360
gtcagtggaa gaatttgaag gtittgattc tccggaattt gaaatgtatt tgtagtcacg 420
gactttcagg attctgtctt taatgacctc tacaaggctg attgtagagt tattggacca 480
ccagttgtat taaattgttc acaaaaagga gagcctttgc ctttttcattg tcgcccgttg 540
tattgtacaa gtatgatgaa tctagtacta tgctttactg gatttaggaa aaaagaagaa 600
ctagtcagggt tgggtgacatt ggtccatcac awgggtggag ttattcgaaa agactttaat 660
tcaaaagkta cmcatttgggt ggcaattgta cacaaggaga aaattcaggg ttgctgtgag 720
tctaggtact ccattatgag 740

```

```

<210> 169
<211> 2038
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (1490)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1508)
<223> n equals a,t,g, or c

```

<220>
 <221> misc feature
 <222> (1979)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1992)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (2010)
 <223> n equals a,t,g, or c

<400> 169
 tcgacccacg acgtccggcg gcgggaagct ggcggcagcg gtcgggtggcg gtggctgagc 60
 agaggacccg gcgggcggcc tcgcgggtca ggacacaatg tttgcacgag gactgaagag 120
 gaaatgtgtt ggccacgagg aagacgtgga gggagccctg gccggcttga agacagtgtc 180
 ctcatcacgc ctgcagcggc agtcgctcct ggacatgtct ctggtgaagt tgcagctttg 240
 ccacatgctt gtggagccca atctgtgccc ctacgtcctc attgccaaca cgggtccggca 300
 gatccaagag gagatgacgc aggatgggac gtggcgccca gtggcacccc aggtctgcaga 360
 gcgggcgccg ytcgaccgct tgggtctccac ggagatcctg tgccgtgcag cgtgggggca 420
 agagggggca catcctgctc ctggcttggg ggacggccac acacaggggc cagtttctga 480
 cctttgcccc gtcacctcag cacaggcacc aaggcacctg cagagcagcg cctgggagat 540
 ggatggccct cgagaaaaca gaggaagctt tcacaagtca cttgatcaga tatttgaaac 600
 gctggagact aaaaaccccc gctgcatgga agagctgttc tcagacgtgg acagccccta 660
 ctacgacctg gacacagtac tgacaggcat gatggggggg gccaggcccg gccctgcga 720
 agggctcgag ggcttggctc cggccacccc rggccctagc tccagctgca agtccgacct 780
 gggcgagctg gaccacgtgg tggagatcct ggtggagacc tgagcaggag ccctgagtgc 840
 tcacagccgc ctctgacgca ttgacacgtg agcactggct cccacggagg gtgcgcctgc 900
 cgccagcggc ccagccttgc tgccctgtct gctgattctg agaaatccca gaacagccca 960
 ttaccagtgg ggctgcagcc tagggccgct ccactcacct cccccctgtg gagggccagg 1020
 cagaggctgt tctggaaggc ttcttgtctt ctgacgtccc cacagccctg ggcccctcgt 1080
 gtctctttgt gtccccact gtagaggacg gtgagccgca gctgcatcaa cctcctttta 1140
 ccttttagata ggtgaatttt tacaattcag ttttacatgt tttgggcagt attttgtctt 1200
 aagatatatt ttttaaaact tttatacctt atctctttag attttttcag ctattttctt 1260
 aaaagtatat tttttctata aacatccctt gctgctacat tagaactttt atagcctaaa 1320
 caattgcagt tgggtgtgtt cattttttta aggtttaaat aagggttttt tgttttgttt 1380
 tgttttttgc agtgagcatc actacagtct cagtcaacag tgtgaatgta tcatgtttta 1440
 ctttaaatgt gtgtgtgata cttcttcatt atgtcctgcg ctgcagtgan gacctgggtg 1500
 aaaatcangg aaccgcacac agccacatct tcctagacct aagagtaaata tatggaggat 1560
 tttattttatg tctattttata tgtaaatgtc attgaagaca aagggtcaaata atttgtctgt 1620
 ttgtagatca caggcaccag ttggtcttca gggacctcat agccccctcg tgggtgccttc 1680
 tcaaggcagt gttcctggag gctcccttca gggtcagccc atgcacctgc cctgrrtgag 1740
 gaagtagcat tgctgctgga tgagaaacgc ctgcgctgct ctgttagact ggtgctgaaa 1800
 caaaagggtta aggttaggtt gaagtctaga atgaaagaaa tctgaatcca tgtcattcat 1860
 aaccccttga tctgtagtgt catgggtgct gccgcagagg aagttgagct gggggtgcct 1920
 gccagccttt ccaactcctgc cccgcttcaa cccaaatgct ccctgtttcc caagctttnc 1980
 ccaaatttcc tnaaccttta accaaaaagn ggggtttcct ttggggcaaa aaggccat 2038

<210> 170
 <211> 522
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (471)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (488)
 <223> n equals a,t,g, or c

<400> 170
 ggcacgaggt taatctaagg tgaagcaaac agaaaattgt ggaggttttg ttggtgtgca 60
 actgaggaac atggctcaag aaactaatca cagccaagtg cctatgcttt gttccactgg 120
 ctgtggattt tatggaaacc ctctgacaaa tggcatgtgt tcagtatgct ataaagaaca 180
 tcttcaaaga cagaatagta gtaatggtag aataagccca cctgcaacct ctgtcagtag 240
 tctgtctgaa tctttaccag ttcaatgcac agatggcagt gtgccagaag cccagtcagc 300
 attagrcctc acatcttcat ctatgcagcc cagccctgtw tcaaatcagt cacttttatac 360
 agaatctgta gcatcttctc aattggacag tacatctgtg gacaaagcag tacctgaaac 420
 agaagatgtg caggcttcag tatcagacac agcacagcag ccactctgaag ngcaaagcaa 480
 gtctcttnaa aaaccgaaac aaaaaaaaaa atcgcttgtt tt 522

<210> 171
 <211> 1666
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (114)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1659)
 <223> n equals a,t,g, or c

<400> 171
 gagtccatct tccaccgcgg ccacgagcgc cttccgcatt gccagcgcct gcctggacga 60
 gctgagctgc gagttmctgc tggctggggc cggagggggc ggggcggggg ccngnccccg 120
 gaccgcatct cccccacgg ggtcggtgcc tggggatcct gtccgcatcc actgcaacat 180
 cacggagtca taccctgctg tgcccccat ctggctcggtg gagtctgatg accctaactt 240
 ggctgctgtc ttggagaggc tgggtggacat aaagaaaggg aataactctgc tattgcagca 300
 tctgaagagg atcatctccg acctgtgtaa actctataac ctccctcagc atccagatgt 360
 ggagatgctg gatcaaccct tgccagcaga gcagtgcaca caggaagacg tgtcttcaga 420
 agatgaagat gaggagatgc ctgaggacac agaagactta gatcactatg aaatgaaaga 480
 ggaagagcca gctgaggggca agaaatctga agatgatggc attggaaaag aaaacttggc 540

100

```

catcctagag aaaattaaaa agaaccagag gcaagattac ttaaattggtg cagtgtcttg 600
ctcgggtgcag gccactgacc ggctgatgaa ggagctcagg gatataatac gatcacagag 660
tttcaaaggc ggaaactatg cagtcgaact cgtgaatgac agtctgtatg attggaatgt 720
caaactcctc aaagttgacc aggacagcgc tttgcacaac gatctccaga tcctcaaaga 780
gaaagaagga gccgacttca ttctacttaa cttttccttt aaagataact ttccctttga 840
cccaccattt gtcagggttg tgtctccagt cctctctgga gggatgttc tgggcggagg 900
ggccatctgc atggaacttc tcaccaaaaca gggctggagc agtgcctact ccatagagtc 960
agtgatcatg cagatcagtg ccacactggt gaaggggaaa gcacgagtgc agtttggagc 1020
caacaaatct caatacagtc tgacaagagc acagcagtc tacaagtcct tgggtgcagat 1080
ccacgaaaaa aacggctggt acacaccccc aaaagaagac ggctaaccct ggagtatcac 1140
ccttcctccc tccccaggca ccaactggacc aattaccttt gaatgctgta tttggatctc 1200
acgctgcctc tgtggttccc tccctcattt ttcttgagc tgatagctct gcctattgca 1260
ggacaatgat ggctattcta aacgctaagg aaaaaaaca aacacagaac tgtttcaagt 1320
actcaagact gacttacaga ccaaccaacc accttgctgg aacccttgct agcaggcatt 1380
cttataaaaag aaactttcga gcctccttat attgctggaa actcagctgt gctccagact 1440
agagcctcct tacctatgct atggattttt aatttatttt ctcttatttc atgtacactg 1500
cttttttttg ttacagtgtg tgatggatgt gtatgaaaaa aatgtatctt tgggaaaaca 1560
attacagttt gttaatttga aaaaaaactc gtgccgaatt caagcagccc gggggatcca 1620
ctagttctag agcggccgcc accgcggttg agggccagnt tttgta 1666

```

<210> 172

<211> 438

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (413)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (438)

<223> n equals a,t,g, or c

<400> 172

```

gcgaggagg tgtatgccc gctgcaaaaa atgcttcttg agcaacaaga gaagtgcctg 60
ctgttctcca agcagttcat gcaccagggc aacgtggctg agaccaccg atttgagaag 120
cttgctcagg accgcaagaa acagctggag atcctgcagc tggcccaggc tcagggcctc 180
macctccca cccaccactt tgagttgaag acattccasa ctgtgaggat cttctcaca 240
ctcaacagca cagaaatgca tctgatcatt gtccggggaa tgaacctccc agccctcca 300
ggggtgactc ccgatgacct ggatgctttt gtgcggtttg agtttacta cctgactcg 360
gaccaagctc aaaaaagcaa aacagctgtg gtgaacaaca caaactctcc cantttgatc 420
actcttcaac taaactcn 438

```

<210> 173

<211> 2511

<212> DNA

<213> Homo sapiens

<220>

101

<221> misc feature
 <222> (12)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (28)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (44)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (2456)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (2488)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (2511)
 <223> n equals a,t,g, or c

<400> 173
 gtaccattcc cngaccgctt ggccctgtncg attaatccgc ccnatagga attggcccg 60
 gccagattcg gccgagcaag cggaacctct gggaaaagca atctgtggat aaggctcactt 120
 cccccactaa ggtttgagac agttccagaa agaaccceag ctcaagacgc aggacgagct 180
 cagttgtaga gggctaattc gctctgtttt gtatttatgt tgatttacta aattgggttc 240
 attatctttt atttttcaat atcccagtaa acccatgtat attatcacta tatttaataa 300
 tcacagtcta gagatgttca tggtaaaagt actgcctttg cacaggagcc tgtttctaaa 360
 gaaaccecatg ctgtgaaata gagacttttc tactgatcat cataactctg tatctgagca 420
 gtgataccaa ccacatctga agtcaacaga agatccaagt ttaaaattgc ctgcggaatg 480
 tgtgcagtat ctagaaaaat gaaccgtagt ttttggtttt ttaaatacag aagtcagtgt 540
 gtttctgcac ttataataa agcatggaag aaattatctt agtaggcaat tgtaacactt 600
 tttgaaagta acccatttca gatttgaaat actgcaataa tggttgtctt taaaaaaaaa 660
 aaagaaatgt actgttaagg tattactttt ttatcatgtg atgattcata tctaaattac 720
 attattatgt tagctgacag tggtagctgat tttttagggtt ggttggtttt tggatttctt 780
 tagtagtgat agtagcctga accacatttt agataactca attatgtatg tatgtgcata 840
 cacatatata aacacactaa tggtagaatg ctttttttatg tgctagacta ttatatattag 900
 tagtatgtca ttgtaactag ccaatatcac agcttttgaa aaattaaaaa atcacactat 960
 attaatattt catatttgcc aacagaaaca tggcagatag gtatcaatat gttttcaatg 1020
 cctgatgacc tataagaaga aagtattgaa agaagagag attagaactg ttagaaggag 1080
 ttgaaatttt ctaaaagaca tagtatttag ttataatta aatgcattct tgaagtccag 1140
 tgtgaatttt attaatgcta tcatctcgac caagctcaaa gcctacttat tagaaacaat 1200
 gaagttcaca ataggtcata aggtctcttc cttttctaaa attgaaagac aagaaattta 1260

102

```

gtgccaatat tgtacagaca gaaattccat gtatgagtct caacaaagac tacctttggc 1320
taaagtgtcta gaagcagaga agtaaagtga gcaaaatcca gtgttgagga gtcattgacag 1380
tactttgatc tttatatact ctgaagcatt tcttcaaact tttctacttt tatttgtcat 1440
tgatacctgt agtaagttga caatgtgggtg aaatttcaaa attatatgta acttctacta 1500
gttttacttt ctcccccaag tcttttttaa ctcattgattt ttacacacac aatccagaac 1560
ttattatata gcctctaagt ctttattctt cacagtagat aatgaaagag tcctccagtg 1620
tcttggcaaa atgttctagt atagctggat acatacagtg gagttctata aactcatacc 1680
tcagtggact taacccaaaat tgtgttagtc tcaattccta ccacactgag ggagcctccc 1740
aaataactat tttcttatct gcagtattcc tccagaagag ctaaccaggg cagggctggc 1800
atgagaagtg acatctgcgt taaaaagtct atcttctcta taagtctgta aagagcaatt 1860
gaatcttcta gcttttagcaa acctaagcca aaggaaggaa agccacgaag aatgcagaag 1920
tcaaaccctc atgacaaagt aggcacaagt ctacaataag ctaaatacaga atttacaaat 1980
acaagtgtcc caggtagcat tgactcccgat cattggagtg aaatggatca aagtttgaat 2040
taaggcctat ggtaaggtaa cattgctttg ttgtactttt gaacaagagc tcctcctgat 2100
cactattaca tatttttcta gaaaatctaa agttcagaag agaattgtatc actgctgact 2160
tttattccaa tatttggatg gagtaagttt tagggtagaa ttttggttcag tttggattta 2220
atcttttgaa aagtaaattc cttgtttact ggtttgacta taattctctg ttatctttac 2280
gaggtaaaac tgcaagctga ctagcatgtt ctgtgaatct gccattccta aaaattttat 2340
aaacacttga tacttttcac tgataatgga tcgctccaat aaacatatat tgtgaaaatg 2400
catccacaat aatggaatt ctttctgca aaaaaaaaaa aaaaaagggc ggccgntcta 2460
gaggatccag gcttacgtac gcgtgccngc gacgtccata gccccttcta n 2511

```

<210> 174

<211> 230

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (227)

<223> n equals a,t,g, or c

<400> 174

```

tccttcccag tgggtacttnt actaaattgt tgtcttggtt ttatttttta aataaactga 60
caaatgacaa aatgggtgagc ttatgatgtt tacataaaaag ttctataagc tgtgtatata 120
gttttttatg taaaatatta aaagactatg atgatgacat taaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanggg 230

```

<210> 175

<211> 1191

<212> DNA

103

<213> Homo sapiens

<220>

<221> misc feature

<222> (44)

<223> n equals a,t,g, or c

<400> 175

```

ggcagagcgg cacgagatgt gagccacat gcctgggtgt ctcttcatt ctttaggcag 60
ttcattgtca cttccttcca ttggtaaaca tgtaaattat agtcgcatga tttagaattt 120
tactgaccaa agtcataata atagttaaca gtacaaggaa ctattttkgt ataatggttt 180
atttaataca gtatacatta tctttcatat actttgttac aatgttaaaa aaacttcatt 240
tttcataata taggaaataa agttggaaac aactctggtg ggaatacttc agatagagca 300
agaaagcatt cacagcaagg cctataatca gtaagatgtg tgaaaagttg ggtagccaca 360
ggaggtgttc attaaggata tgattccatt tatatagcta tttctattgc ataaccagga 420
cagttttatt gttttgaggt caatgttctt ttaaaatttg attttctgta agaagaggct 480
ttttggccca gaaagcctta cttattttac awcttccagt ttgtccatcc catgagttag 540
agttcgtctt gactctgcaa gctagaatca aagaattatg aaagtaagat catttagatt 600
tgaccaaggg caccattaaa tgggtgtcagg ttttaggaag cagacgggtg tataaaaaga 660
aaatgaacaa agatttcact tattggggat caggcataac tggatgcctg gattgtcctg 720
ccaccagct gccaccaata aaatcattca tctactctgca agagggacca gatgcttcca 780
tcatcagtac tccttgtttt tctgttatct cctttgaggt agctaaaaat ggcagccaaa 840
aaaaaatgtt gaggcctttt tcaagtatat actcatgtta ttttgcagaa gataggggtca 900
ayttcttcag ttgagttatc tgaaagtgtt gggcagtgac accatgccaa aactgttaa 960
attcatgcc a ttaaaaacag tggagtgttc tgcaaagccc gattctctgc agctttaaga 1020
ctggacagta ttgaaatatt cacaggaatc ttccaagccg tgaaagctta atattaaaca 1080
gcccttttaa ttgcaaagga gaaaaaatg gagacacttg tgaaaccttg cattctgagt 1140
gctgccacaa ataaattaag gaattccaga atttcttcat ctacttctgc a 1191

```

<210> 176

<211> 1499

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1462)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1476)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1495)

<223> n equals a,t,g, or c

<400> 176

```

gccttctccc gcctccctcg gccttagcca tggcgagtag cggcggtgct ggggcggcgg 60

```

104

```

cggcggccgc ggcggcgaat ctgaatgcgg tgcgggagac catggamggc tgctgaaaat 120
atgacaagct gactttctgg agaaattctg atgagatatg tcaagctctg caagrpgggt 180
tgaagattgc attgtagttg agaatgtaca wtgaaattwc tgcattgcagc agtgtagaaa 240
aattttmctt tttaaaagaa ttataaaacc atagctttat aaatcagtgg aaagtggctt 300
acagagagaa ctatcagatg tgtttacatc acatcttatt cacttttttt aacagctcta 360
atgctttggc attgctatgk tcataattat gtattcctta tttatagctc tgatagcttt 420
aattttctaa gcagtctgtc tatcagatgt gcacatctgc tgtgccaggc tgaagtatag 480
tggaacccat cagtagtaat gtgtagtagt tatgacttgt tgacatttcc attataaact 540
ttaattttga attgtttatg cattataact gtggatttat attgtattgg gctgaagttg 600
acaggatttc agccaccact tgtgaatttt tatttagatt cattatgtat atcagaatct 660
tggtttttga aataagagca tggaaaacat ttcttgaat ctactcttga acaaagaata 720
tttagttttt caaacagttt gttgggcagc taatagtgtg aaccaggctc tttttgtatt 780
gagtaaaaaa atcaaacctt gagaaacttg gattttaaaa gtaatgacaa tgcttagggt 840
agtattattt gtaatttgaa tcatttacat ctaatgagaa tgttagttga gaatgttttc 900
ttaaagtttt atatcctata aataacggaa taaaaaaatt tgtaaaatga aacaacaaac 960
atgcaaaatt cctattttact tttattacat aaaagtaatt ttagtgctta cctaataaat 1020
cttgaatggg tatttaataa attattagat ggggtgatgtg tttcaaaaga tacttgctat 1080
tttttgaaga aataagggat ttccagtcac taaacaaaac taaacaatct tattagaggg 1140
tgatgtgttt caaaggatac ttgctatttt ttgaagaaat aaggattcca gtcattaaac 1200
aaaactaaac aatcaaattg tctatattag gaatctcaag tatggctttt tttaaaaaac 1260
cttttttaaca tcttgatgtc aaggattata agtatggctt ttcagaattg ttttgtttgt 1320
cattattctt gccttttaaaa ttttaactca tcaaagtga gattagaaat aaattttagg 1380
aaaatgtagg aatagtattg attctgtccc tgtaatatga atctcagtgg gggtttttttg 1440
caaaactaat atgggttttc anctgatattt aagtanttcc ttgaaatttt tgggnnttta 1499

```

<210> 177

<211> 1538

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (727)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1218)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1487)

<223> n equals a,t,g, or c

<400> 177

105

```

tgtaccggga cctgcagccc gtgggctcgg gcgcctacgg cgcggtgtgn tcgtccgtgg 60
acggcgccacc gscgctaagg tggccatcaa gaakctgtat cgkcccttcc agtccgagct 120
gttcgccaag cgcgcctacc gcgagctgcg cctgctcaag cacatgcgcc acgagaacgt 180
gatcggkctg ctggacgtat tcaactcctga tgagaccctg gatgacttca cggactttta 240
cctggtgatg ccgttcatgg gcaccgacct gggcaagctc atgaaacatg rgaagctagg 300
cgaggaccgg atccagttcc tcgtgtacca gatgstgaag ggggtgaggt atatccacgc 360
tgccggcatc atccacagag acctgaagcc cggyaacctg gctgtgaacg aagactgtga 420
gctgaagatc ctggacttcc gcctggccag gcaggcagac agtgagatga ctgggtacgt 480
ggtgaccggg tggtagcggg ctcccagggt catcttgaat tggatgcgct acacgcagac 540
ggtggacatc tggtagcggg gctgcatcat ggaggagatg atcacaggca agacgtgttt 600
caagggcagc gaccacctgg accagctgaa ggagatcatg aaggtgacgg ggacgcctcc 660
ggctgagttt gtgcagcggc tgcagagcga tgaggccaag aactacatga agggcctccc 720
cgaattngka gaagaaggat ttgtcctcta tcctgaccaa tgcaagccct ctggctgtga 780
acctcctgga gaagatgctg gtgctggacg cggagcagcg ggtgacggca ggcgagggcg 840
tggcccatcc ctacttcgag tccctgcacg acacggaaga tgagccccag gtccagaagt 900
atgatgactc ctttgacgac gttgaccgca cactggatga atggaagcgt gttacttaca 960
aagaggtgct cagcttcaag cctccccggc agctggggggc caggggtctcc aaggagacgc 1020
ctctgtgaag atctctgggc tccgggggtg cagtgaggac caccttcacc ttccacctga 1080
gaggggactc tcgttgccac cttgaccttg gctggggcctt gcattcccaag gcatccatca 1140
gagcagacgc ccgggttcca tggaccctcc tccccacggc catgcctctg ctcttggggcg 1200
cccatcatgg aggagcanct gaactttctg gacaagacct ctggccgacc tggggatggc 1260
ctctgatycg tggagcagtg gccacttgc ccggtgctct cagaaacctc agagctgggtg 1320
gggctccaga tcagccttgg cctctgagcc ctgcctgctc tggggccatgc agaggaagga 1380
cagaggggtg gcgcagggca ccaactcagg gacatccctc ctcttggggc acgtcagttg 1440
accttctctg acccccagcc tggaatgtaa atcagctgtg tggtagcncgc gtggctggaa 1500
ggaaatagac cctttttagt ctccctgaaa aaaaaaaaa 1538

```

<210> 178

<211> 896

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (194)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (825)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (828)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (831)

<223> n equals a,t,g, or c

106

<400> 178

```

ggacgcgtgg gctgcacctc accttgtcca cgtaccagcg caatacctgg ggtgacttct 60
tagaggccat actgcctctg gcagtgcagg ctgcaatgga agaaaatgtg gagtttcgga 120
ggggtctgcc ccgagacttc atggattaca tgggggcccc gcattcagat tctaaggatc 180
cgggaaaaaa ccgntttcat ggagaagggtg cgggtcttgg ttgcccgcct gggacacttt 240
gctcctgttg atgctgtggc cgaccagcga gccaaagact tcattcacga ttctctgccc 300
cctgttttga ctgataggga gagggcacta agtgtttacg ggcttycaat tcgctgggag 360
gctggagAAC ctgtaaACgt gggggcccag ttgacaacag aaacagaagt ccatatgctt 420
caggatggga tagctcggct ggtgggtgag gggggccatt tgtttctcta ttacacagtg 480
gaaaactccc gtgtgtatca tctggaagaa cccaagtgtc ttgaaatata cccccagcaa 540
gctgatgcca tggaactgtt gcttggttct tatccagagt ttgtgagagt gggggacctg 600
ccctgtgaca gtgtggagga ccagctgtcc ttggcaacca cgttgatga taaggggctg 660
ctgctcacta agatgcctct agccctaaat tagtttcttg ttgattgctg gaaacaaggc 720
agtagtgatt ctccgctgcc actgctaact tttttttttt ttttttttct cttaaactca 780
agttcttacc ttgataagca tcagtgtgct cacatttacc tttancantg ntcagtgtca 840
caaacctcgg aagggtctcta ggaagaacca tctcatctag gtacaaaagg gaaagg 896

```

<210> 179

<211> 568

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (469)

<223> n equals a,t,g, or c

<400> 179

```

ttatcttaga tttctagtta tttatatatt aactttttgt ttattcagaa tcattttcct 60
gtttgtngga atattttctaa gagccttggg aaaatctcga gtaaaatttt aaatgaaatt 120
tgtatagtgt tctgcctctt tccaaaggta tttctcaaaa ttgggaattg ttttattatt 180
gaagttagaat gacttcaggg gaactctaaa atgcaagatg ggaagcttct gtttggtttt 240
ttcctttccc tttggttaagg tcttttgctt cccatcccc tgaaccacct ttgtgctgtc 300
tgttgtccag tctgctctcc kgatccctaa rgakgtttct tatctaggct gccatttatg 360
tggtgaaaaa acaaggtaga aaatactctt ctgtatcttg tatcaagggt taatctaattg 420
tcttcatcac tttgttttga ratatttttg aatgttatcm acaattatna tagatggagc 480
atgtatgtct taggtttggt gttaatgttt aacatgcatt atcttattca atcctcacag 540
cagtcataaa atgtaggtgt ttagagg 568

```

<210> 180

<211> 428

<212> DNA

<213> Homo sapiens

<220>

107

<221> misc feature
 <222> (405)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (413)
 <223> n equals a,t,g, or c

<400> 180
 aaacacctat ggaaataatt ttgttttttt ttttttaaaa aggaatgaga tcatgtcctt 60
 tgcagggaca tggatgaagc tgggaaccatt atcctcagca aactaacaga ggagcaggaa 120
 accaaacacc acatgttctc acttgtaagc ggaactgaac aatgagaaca cacggacaca 180
 gggatgagat caacacacac tggggcctga tgcaggggcc gtagegggga gagcatcagg 240
 ataactagct aatgcatgtg gggcttaata cctaggtgat aggttgatag gtgcagcaaa 300
 ccaccatggg acacgtttac ctatgtaaca aaccgcacat cctgcaattg tatccagaac 360
 ttwaaatatt ttaaaaayct ttagagawtm caaaaaaaaaa ggttnttcaa tgnntcccca 420
 ttaaattg 428

<210> 181
 <211> 2901
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (10)
 <223> n equals a,t,g, or c

<400> 181
 agagaaaagcn ttccattgaa aggtagatac tttgaggagt aaaaagactt ctttgaatgc 60
 tggtaaacac cgcatttatt ttgtgtatgc agtttgattt gcacatgtat aaatggagat 120
 gcttttcatt tttgtttgga ctgggtttgt gtcactgtct attacagttt gcttttttgt 180
 gtgtttgtctg tgcgtttgga gatattagtc agtttcttta gtgatatttg tttccttgat 240
 gtgccttttc gtttttcttt ggggtttttg gaatctggat gctgttgaag ggcaatagca 300
 gactcctcca gctaagagac aggacatgtt cttgagccac tgtagctgtt gaagctggac 360
 accagacgct ccctataacc ccccccgccag gccatagcgt gwatgcawgt gcacttccac 420
 ccacagagga ggggtgtgaag ccttgagaac ctcaagaaaag ggctggattc tgccatacct 480
 ttgggtctac cttgggactg ctgggttgcca acgtgtcaac cagcctgtgt tccctgccac 540
 ccacgcactt gctgaggtgt ggctgargca gaatcatgtg aatgggtgca tccaaggagt 600
 tcagggccct gcttgagaga gaaatamttt agcatcatga aagggaaaga acgtgcaccc 660
 cttttttgtt tcttttagtga atgcaagatt taataaaagt gaataatgag cttccccctt 720
 gggagtggag ccacagtgcag ctcaactgaca gggttgacat cagtatgatg tgttggactg 780
 aaactgtatg tctgtaggta ggtgtgtgcc ttttagggca gaccacggtg gccaccccat 840
 ttctccaagg tggtttacct agcttgtgta tattagacat tgccaccctc acctctggcc 900
 aaaaattctt gatttaaaaa gaaaagtcta ttttgtaaac gacaggctct gttgtatgtg 960
 ttactatccc aagcctggat tattttattt atttaaaagt attttaattt ccatattggc 1020
 tttattctaa tcccatccat ccctgtggag ctgcagagca tcttcatgtg agtagacgga 1080
 tggacataaa tagattcatg ctcathtagt aagctgggag tttcgtgaag ctgaggggtga 1140
 gttcctgtga ttcttgttcg cttcaacaaa aagtgggaga ccaagttttt atagcaaaaag 1200
 accaaaattag ctgtagagtc ttgaatgcag aaaaaaatta ccctagcttt cttagcactt 1260

108

```

agggttttgt gaggattcag tgttttagcac agtgcttggc catagtaagc cctagtaaat 1320
gttaaataatt gttattagt tttcgtaaaa cttgagaaat agagctgagc tcattccctt 1380
cctgttgatt caaaaataat acctacatga aaacatgatt ccaagttgat tgaatgttgt 1440
aggaattact ggttttagagt agcccagttc tcggcctacc ctgctgggtg ggatcttact 1500
gtattcttga atgcactggt ttgaaaatat gccagacttc agccccaag gaaacaaggc 1560
tgcaagaatt tatgaactcc agctggaaaa ggtaaagggtg acctttggct agccacatac 1620
tggaccttac cccactgacg tctttcagaa cattccaagg gttttcctca aggaacattt 1680
ttgagctaga aattaaaatg ggttctcttg cagactgcac cccttgagtc aaagttaaca 1740
gtattccttt gaatgcaata atagaggctt ttctgcgtta agggagaagg aatgaccaat 1800
tgaacttaca cattccccag gcaggctcct ttgccggccc ctacaggctg ggggtggcccc 1860
tcctgtcctc agggatcaga ctcccagact ggtagttct gcattgttcc atcaaattaa 1920
aggttattcc ctggccgcct cctggagaaa accaacccca ccctgccagc tgggggcaat 1980
ggggcaggga ttttggcctc tcagaacagc tcctagaggc tgctcatgac tgaatgtttt 2040
cccaaatcac ctaaatatcg gtttgccttt tgttttgggg gagaggattt agcctcttac 2100
ttccctgatg gattcaaagt tttatctatc tccttatctc ctgccctgtc ttggcacaaac 2160
tctggataga ttgcagggtg ggaatttgcg ggagtttggg gacttcgtca aattcctttg 2220
gattctgttc cgccaaatca gcagtctcgt cctgtggatg cagtgactgg aatttcccat 2280
ctgcaaagca tctctgtagc ccagattttg tggagcctta agacactccc tcaatgccac 2340
cctgacccca cggctggaga accctgtgct tatgtggtgg gcagggccac tgttgatgga 2400
ggatggcggg gacggggtgg tgctcaaagg atctgtggtg ctggagggtc acacgcctct 2460
caggacagcg tgtcaggaac ctccagagcag cttcacatct gccaaagctg agagggagcg 2520
aacttgggaa gcattttgct cattgtccta cccaagtatt aatagcataa tagttgatgc 2580
caaaggagat ggtgacgtcc cttccactgt agttgctgtc acaaccttga cgtctttaag 2640
ctaattggccg tttgcatctg tgtcttcaaa cagatcctgg ttacagccat tttgtgtgat 2700
tcacttcggg ggttaagtaa tgcaggattc tgcaaacaag gtgtcgccgt ccaaattgtac 2760
tgtcctggca tagagagcac tgctttgttt tccactgttg tagagaaaac tagggagAAC 2820
tttatttttc aataaacttt tcttgtgtga aaaaaaaaaa aaaaaaactc gagggggtgc 2880
ccgtacccaa ttcgccctat c 2901

```

<210> 182

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (276)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (286)

<223> n equals a,t,g, or c

<400> 182

```

taatttaggt gacactatag aaggtagcc tgcaggtagc ggtccggaat tccccgggtcg 60
accacgcgt ccgataaaac atgattttgt tttctaccct tcaaggtaaa cattaaaaat 120
aargtggtac ttgtgtwctt gtwcataaaa ccaaaattat akttgggaaa aaaataaatt 180
tatatatgaa aatgtcaaaa tcatttttaa agtattatatt tcaaataaaa tggagaagct 240
ggtgaaaarw maaaaaaaaa aaaaaaaaaa aagggngccc cttttngggg 290

```

109

<210> 183
 <211> 641
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (14)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (43)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (55)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (68)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (80)
 <223> n equals a,t,g, or c

<400> 183
 gttcaggaaa cccncaaggg ggggggagtc caaacgggat gcnaggggaa gcttnccttt 60
 tcccagcnaa tttgtgttcn ggtttgaaaa gacccaccac aaagctttty ctatcttctg 120
 atttaaaagt cgcttttgaa tatgaccatg agaaaccaag aaatgctgct tgtgtggtgc 180
 tctgcttcct gaggatttgg ctggaagggg attctcctgt ggcacatggg agaaggccat 240
 cttctgtgtc ggtgctgtga tctgccttgt tctcacttgc tgaggataag ggcatacacg 300
 ctgctcctcg ctttcttgtt gcccgacttc gtactaagca gctcaggagc agtcactcag 360
 acccaaagtgt cttgactgtg ttgtttttta tcaactgtgac ccttaaagta caggccaagt 420
 gttgtcaaac accttggtta aaacagtggg ggggtgatggg taaagcagta gagggccctc 480
 aaccacaca ctggctgaaa ctgccaccaa ctgccacgat gaacccaact gctgtttatg 540
 ccccatcttt cctttttttg tatctacacc cacacgattc ccaatgttgg atatttctac 600
 atgaataaag caaggatcag tgccctcttat gtaaaaaaaaa a 641

<210> 184
 <211> 522
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (514)

110

<223> n equals a,t,g, or c

<400> 184

```

caccacgtgg ctgtgaaaat gacaaagcat ggtcgtgagc cactatgccc ggccggattt 60
gcccttatta atggttattt cttgtgaaag tttctttttg cctttgcatt ccttttattc 120
tgttttattcc cccatgcctc acccaaagag ttgcacggtc aattggcccg tgaaggggac 180
gcctactttc aaacaaggca gacaggacac gacaggacgg cggctcatag cacagacttt 240
ggattgcagt ggatgggacc agatcctggc tccacttcts gcyagctgtg tggccctggg 300
caagctgctt aacctctctg ggccctcagtt tctccccctg taaactgggg gatgtgaaca 360
gggcctgcct ccgagtccta aggattggga gtagtcgtgt aaagtgtca ggtccacagg 420
ccatcaatac taatagttaa aaattattct tagaatcttg cttccctcag ctccctgaaa 480
ggccactaag gcaccccgat tgcagaggcc aatnggtccg gg 522

```

<210> 185

<211> 735

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (197)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (293)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (386)

<223> n equals a,t,g, or c

<400> 185

```

agtataacca tttagggtgcc agatttgata atcaccagck gctcatksar gtcctatggt 60
gcaaagttac tcttacscct tttttacatt rcttgataaa ggcaatsttt aattayrtat 120
tityctrtta ctagctggta gagttcatac cttaaagtcag taaataatgt taagaatttt 180
ttccagctga gcaaatngta tgtatctagt tgtaagaaat caagaagagg atataaaaata 240
taatcaggat gtggactcta aaacggaata acctctatgt cctgtaactt ttntcactyg 300
taataataca gcattctcac cctrttaaat ggaaatttar agcaccttta aattccggaa 360
taaaattgct atttggatwg aaaaanccct taggcaacat ttattgaata ttaggaaata 420
acttttatgg gattagaatc cattttttat agaaacccaaa tttaaaagta tacatatttt 480
aatataagtg ttgtgataat acagtaacca aaattgaaca cacagtttta wagcttttta 540
tatttagtag cagttgaata tatatggcat gttttacata gattaatttt actatttttc 600
tttrttttaa maagagracc aaattgaaag ccracagata ctgcaratga ctgggatttt 660
tgtttctgyc ttatcttttt gtgttttttt tctgaataaa atattcagag gaaatgcttt 720
tacagaaaaa aaaaa 735

```

<210> 186

<211> 785

<212> DNA

111

<213> Homo sapiens

<400> 186

```

aattcggcac gagagcaagc ggaaccaggt atcgtacgtg cggccagccg agccggcggt 60
tctggccccg ttcaaggaac gggtcggcta cagggagggg cccaccgtag agactaagag 120
aattcagcct cagccccag atgaagatgg ggatcacagt gacaaagaag atgaacagcc 180
tcaagtgggtg gttttaaaaa agggagacct gtcagttgaa gaagtcatga aaattaaagc 240
agaaataaag gctgccaag cagatgaaga accaactcca gccgatggaa gaatcatata 300
tcgaaaacca gtcaagcatc cctcagatga aaaatattca ggtttaacag caagctcaaa 360
aaagaagaag ccaaatgaag atgaagtaaa tcaggactcg gtcaaaaaga actcacaaaa 420
acaaattaaa aatagtagcc tcctttcttt tgacaacgaa gatgaaaatg agtaagtgt 480
aatattttga atttagtcta ctttgaaagt atatggagtg ttcattaaaa tcacattttt 540
tcctattata agatactac aagttcttta tagaaagttt aggaaataga gaaaaaaatt 600
taataaacta catctattca tcaatacccc tctgacttaa aatgccaaact ctatagaaat 660
tagctagtat taacattttg ttatttcctt tgtgtggttg tatatatatg taaattatat 720
ttttaagcaa aatacatttt ttgtgtgtaa acaaaatttt ataaatacaa ctgtattgca 780
aaaaa 785

```

<210> 187

<211> 1679

<212> DNA

<213> Homo sapiens

<400> 187

```

gatcttttagg tttttcctat agaaaacatt ctctctccat cagtagccct ttatttgata 60
ttcagaagtg gaaagctttt tcattctcca gtagaacttt taaaaattgt tacagataacc 120
tagctcttca cagatatcat gtattgtaaa cagtcagtgt tcttaatttt attttctcta 180
tttgagtgca taattatcct aataatccca aagacactga caactcaagg aacagcagta 240
cagtactatt agaagttaag tatgttgttg ttatttcaca tttcatttaa ttgtggataa 300
atgttagaca tctgttgaaa taagtcata tgggtggaaac gacaactata ttatgaatta 360
ttttcagaaa tggatctttg aatagcagat caggatttaa ataataaaat tatctatgaa 420
tcacttttat ggatcatatc atatgatata aatccagagt tattggtgca gaaatggcta 480
cccgagagct tggtaaatTT gccttgggtt cttatgttaa atgtattgtg cttcccttct 540
gtctctagaa tgtggctctt cagaagacag acaatcgaca tttaaatTTt tccaaacaat 600
gaaaaactaa attaaaaaca ttgcttgata tttcatttaa aattgcacct tgcttaagggt 660
ttactgaata actgaaatgt cagcaattta aaataaattc aattgtgtga taaaatatct 720
cacctataat agaagaaaag gaaaatcata ttatttggca attttgcagc attgtgggtg 780
cctaacaggt atatccagca gatgagaaac agtatgaaag gattgtatta acatggtaag 840
ttttgcccct aggaaaacga tcttgcattc tggattcttg cagcaaagtc tcagatactt 900
aatacgTTTT cttgktttat catctgktct atgattcggc ttcactttgt gtggktattg 960
aattatgtaa cagagatttg gktttcccaa aatgktatca catttgaaac tatgattgct 1020
ttgkgktcag tccttttggg acacgtagct tycagcttaa gggtagagga aatatatacc 1080
taaaatcatc aatacatgaa agaaaaagga tggaaactat gtcctcagtt ttacttctac 1140
caaaacatcc ctgtatgtgt gtgcatgtat gttggcggtg gtgtgtgtgc atgcatatta 1200
gtaaatgtgt gtttgcatgt gtgtgttggg gagtgtatgt gatctgggtg tttgtttatc 1260
tctgttatta ttccccTTta gctttatttt agtcaactct acattatgat gaatttcaaa 1320
atgaagctgt attaaaataa ttgtaataata acaattcaat ctcacatggt actgcagata 1380
gttaactTTTT gctgcaatct attgtacatt tgcaattttc tgtgttagta aacttagcag 1440
aatctgggtt wttattttwg tgtaggctta atgttccactg aaagataagt caattactgy 1500
tagtaaaaaa ttaagggtact ctactgcag agatttaagc ctgggcctaa tgtgctgtat 1560
tatgaagcct tgtgactgaa aaatatgttt acatatgttg tctattTTTT taataaactt 1620

```

112

ttatagctgg tctatttgct cagtaaaaaa aaaaaaaaaa aaaaaaaaaa aaactcgag 1679

<210> 188

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<400> 188

```
cggtgggctc gcgttgaggc tgcggtcatg gagggagcag gagctggatc cggcttccgg 60
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120
ggggacgcgc tgcagctcat ggtggagttg ctgaaggctc tcgttgtgga agcagcagtc 180
cgcggcgtgc ggcaggccca ggcagaagac gcgctccgtg tggacgtgga ccagctggag 240
aaggtgcttc gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300
agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360
agggaaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480
gtgtgggaag gggcagcacc tggggagtcc ctgcctctcc tccctgggac aatagtgtgc 540
atgccacccg gggtcctaca ggcagggtgt gggaaaggcc tggccagcag gtagcctgtg 600
tgtttgacaa acagcagctg gcagcgtgc ctccctgccc cattcctgcc acccgacatc 660
aaagctggcg tgtgaccttt ccagccatgc gatattcccc ttggaagatg cttccccagg 720
ctataaaatth gttctcacaa agcaacatca ataaatcaaa actgtctcty ccaaaaaaaaa 780
```

<210> 189

<211> 533

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (485)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (498)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (522)

<223> n equals a,t,g, or c

<400> 189

```
ggtcccttta aggtttgctt ctacagcccc tggacttttag cctaaacacg gacccgcgaa 60
gctggcttta tttgtccatg tctcggacag agcctgggaa gctgccagtg agatttcaga 120
gaccaagagc gcgaaggggc gggcgatgtg gcaatccgtc tgggatgtga aaagcgtgga 180
```

113

```

gcgcatTTtag aggcattcga cgaaaacaca ggaaatcact cctctcccgc tcttgggCGc 240
cgctgccact ggggcagagg actgggaacc gcggcagcgg gataagtggc ccagccagag 300
agcgcagctc ccgcgcccgg tcttgccctg cgaaccacgc ggccccctgg gctgaagctg 360
ctccggccat ggccctcggc ccgcgcccgg ccargggty gctgtccct gcttgctggg 420
ctctccctg gtacattgcc tctcccgga cacaattac tccctgaaaa aaaggccctt 480
tgttnaacct actgtggnta accgccttc aaaaactaaa anttgctggg gaa 533

```

<210> 190

<211> 602

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (548)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (600)

<223> n equals a,t,g, or c

<400> 190

```

tccttaatct tggttttcct taaactttct ataagtccag catctgaaat attttgtcaa 60
ttatcacatt aatgtgttca ttttgtaagt aagagtactc aatttaaaat gatcttactt 120
taaaagtggc ctagtttgca gtgcccagca ggacactgac agtcacagct gtgtgacttt 180
ttgtgggtta cttaatTTTT ttgagcctcc ttttctcttc tattcaatga ggataatagg 240
gcctacctca taggattatw atgcattccc ctctgttaat gcacgtaaag tttttacttg 300
gaaaactaac tcaccattta acaaccattc taagcaccat agaatatatt ttgtttcaca 360
aatTTggtat tcattcagaa taagtatttg aaaagtgagt aaattctatg caattatagt 420
tattaaatga cttataaaact gtgtttctct tccacttctt gctacattta atcttctagg 480
tgttcagata tctttggaga ttataggcag caataaagct aaggcagcta acctttaaca 540
ttcttgnggt caagctaata ttttggtgaa aggggaattct tgnggttctn aaaaaacttn 600
ga 602

```

<210> 191

<211> 858

<212> DNA

<213> Homo sapiens

<220>

114

<221> misc feature
 <222> (772)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (801)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (814)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (815)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (852)
 <223> n equals a,t,g, or c

<400> 191
 cttggctcaa acaatatattt ccctataaca aaggcaatag gacacaaaat tcacatcctg 60
 ctgggccttt tttcatcaag tcagggtgat ataaaaacat tggaagtctt ttcaccaaac 120
 cctgacttta ttgaatgcta gtagaagatg tagaattaga gacatctgat ttgtttatca 180
 ccttagcaga aaaaccacag tccaaaagac aagcaaatta agaatggagc ttaaccatgc 240
 ctccattggg aagtctagac tttgagccag gtacagtaag aaaaattagc ctctgattca 300
 ttaagtttgc cacatgactt attttgatat tttggataca ttaactcact taggagaatt 360
 cagaaaagaa tgggtgatta aagttcatta cagctgaata aatgtgtcta aaacagactc 420
 ttgtattctg aaagtacagt ctacaactga taaaacctta tgattctttt ctccccatt 480
 atgcccctat atatatcaag atttgggtac tttatttttag tagaaaatat atatctttta 540
 catatgtatg tattttataaa tgcataagata tatgtataaa aatttgtaag cgtttagcggc 600
 attaattcac caatgcattt ggacaacttg atgtaactga ctttatttta tgtgactata 660
 ataaaaagca taattttctc aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgctcta 720
 gaggatccaa gcttacgtac gcgtgcatgc gacgtcatag ctcttctata gngtcaccta 780
 aattcaattc actggcccggt ngttttacaa cgtnntgact gggaaaaccc tggcgttacc 840
 caacttaatc gncttgca 858

<210> 192
 <211> 667
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (82)
 <223> n equals a,t,g, or c

115

<220>
<221> misc feature
<222> (234)
<223> n equals a,t,g, or c

<400> 192
gcgggggaag cggggctgta gctgggcagg gagagggcgg acgaaatcgg tagcgatctc 60
ggctgcggcg ctgcccactt gncccgcccc gcggggcgcg ccctgaccct tcatctttgg 120
gcaggctcga gggcgcgcg acggttggcg ttctggggcc tcaaactcct gggccttgac 180
cgggcaggcc gcgtctcccc ggggtgtgagt ccaccgggac cgggccgccg cctnaagcgc 240
gkgcgccaca gaagcggcgg cgcccgaaga cgcgctcctg gctcggcccc acagcctcgc 300
ttggccgcca gttcttctgc agccgaaggc ggttggttctt ttaaagaatt attgaagacg 360
aagggtttttt tctttttatt tttttaatgg ytttacagaa tcttaaataa aatacagttt 420
gacatgacgg caaaaaatgt tggtttgact tccacaaatg cagaagtaag aggatttata 480
gatcagaatc tcagtccaac aaaaggcaac atttcatttg ttgcatttcc agtttccaat 540
accaactcac ctacaaagat tttaacaaaa accttaggac caataaatgt gaatgttgga 600
cccaaatgt gatagaaaac gggctagaaa atttatagac tctgattttt cagaaagtaa 660
acgaagc 667

<210> 193
<211> 537
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (85)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (511)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (537)
<223> n equals a,t,g, or c

<400> 193
gttacgcctc tataccggca gcagccgcgg agagcatgcc ccgccccctg ggagcccacc 60
ccgggcgggt aacctcgggt ctcantcccg ggctgtgacc ctccccgagg ccccgcccc 120
acggcgaaag cccggggcag ttaacccttc tcttgctgcg gcagagtcgg caccggggca 180
ggcccatctc agaattaacg ctttgatggc atcaccgcgt cgggaatccc tggggatggg 240
gttctccacc gtcaagacct ttgagccgcc tgagcgacta actcctgcgc ccctgagggg 300
acattttatt cagaaattaa atcattcaga gttccagcac tgtcgggggt catcgggctc 360
tgtccaccgc catagcctag cattgtcacc aacggagcca trgagggacc tcggcccaag 420
ctggggcctc ttcatgtgcg aaaaggcctc ttgccagacc aggatctgtg ggcgcggcca 480
ggctggagga ctagggcggt ggcagtggca ngtgagtga catggctgtg ggtggtn 537

<210> 194

116

<211> 400
 <212> DNA
 <213> Homo sapiens

<400> 194
 tctaactata ttaaaaaatt tctgtatggg gatatcatta ggaaggggat cagtaccttg 60
 tctgtwatgt gtctactaag caaaacccaa actgcagcac cccctgtgg tacactgcac 120
 ctccagtttg tactgggggt tgttgggccag gctataggca tctttcacag gtccttgctt 180
 agcatcccaa gtactgtgaa tacatgttga ttctttaaaa agacctggat tccaactcaa 240
 ataaatcaca tcataatact ggcagagatc atcccaggaa atccaaaata ttccgttgctc 300
 tatttttctga gctgttcggg gatcaaagtt taaatacttt tgcaactctg gagtccagtt 360
 ttttacatca ttttactgt atcttccttt ccaacgtaac 400

<210> 195
 <211> 431
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (411)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (417)
 <223> n equals a,t,g, or c

<400> 195
 cgcgtgggcg gacgcgtggg gtgaattttc agccctcaga gcagaaaatg agaaaataaa 60
 actcgaacta catcagttaa aacaacaagt aatggatgaa gtgatcaaag tccgaacaga 120
 taccaaatta gacttcaacc tagaaaagag cagagtaaaa gaattgtatt cattgaacga 180
 aaagaagctg ctggaattga gaacagaaat agtggcattg catgcccagc aagatcgggc 240
 ccttaccag acagacagga agatcgaaac tgaggttgct ggcctcaaaa ccatgcttga 300
 gtcacacaag cttgataata ttaaataatt agcagggtct atwtttacst gcytaacagt 360
 agctctggga ttttatcgcc tgtggatcta ataaagtgtc tatttaaagg ngaaaaanaa 420
 aaaaaaaaaa g 431

<210> 196
 <211> 417
 <212> DNA
 <213> Homo sapiens

<400> 196
 tttcactttc tacttttttc attttgttct gttcgaattt tttataagta tgtattactt 60
 ttgtaatcag aattttttaga aagtattttg ctgatttaaa ggcttaggca tgttcaaacy 120
 cctgcaaaac tacttatcac tcagcttttag tttttctaat ccaagaaggc agggcagtta 180
 accttttttg tgccaatgtg aaatgtaaat gatttttatgt ttttctctgt ttgtggatga 240
 araatatatt tgagtggtag ttttttgaca ggtagaccat gtcttatctt gtttcaaaat 300
 aagtattttc gattttgtaa aatgaaatat aaaatatgtc tcagatcttc caattaatta 360
 gtaaggattc atccttaate cttgctagtt taagcctgcc taagtcaact actaaaa 417

117

<210> 197
 <211> 734
 <212> DNA
 <213> Homo sapiens

<400> 197
 agacatattg aggtgcctgc ctttgtggag tattcatttt atgctgcca agatatcatt 60
 taatttagac ttaacaagta tttccttggtg attatattac tctgtccttg ttaataaagt 120
 gctgctgtgt ttgactctga acatactacc aaaacttctt caaagagttt tttatgaaag 180
 actttcctcc tttacaagar agaaatruggg tgctgccttt ctgttttagta aaagcagaat 240
 ttgcagtggc atctaaagag acttttttaa ataaaaatta tgtattgtgg cataatcctt 300
 tttttgagct ctacagagaa cagtcttttg gtaatagtgg caggatatta ttccttctga 360
 atatatacc cattatagga ataactgtta cttatttagg attccatcat tgaaaatttt 420
 gaccaaggc acagcagtga aatttatagt tcycaattta gttgtcatta ttgacaggca 480
 ttggtattat tagtcattgc taagcaacta aaacttcac agttcaaata agttttaatt 540
 gtcaaagaa gtataaacac atgaactttc tagaaatatt tcctcttttg gataggctct 600
 taaccagttc atatatatac tttgtcaaat atatggatgt gtatgtgtac atttataaga 660
 accagtatgg atacatccat tcactgtggt acatttttaa ataaaatatt ttagcagtga 720
 atatggaaaa aaaa 734

<210> 198
 <211> 606
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (144)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (155)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (598)
 <223> n equals a,t,g, or c

<400> 198
 aggaagctgg gggaccattt tgcaccatga gtttgtgaaa aatctggatt aaaaaattac 60
 tcttccagtg ttttctcatg cmaaatttyc tyctarcatg tgataatgag taaactaaaa 120
 ctatttycag cttttcctca attnacattt tggtngtata cttcagagtg atgttatcta 180
 agtttaagta gtttaagtat gttaaagtgt gatcttttac accacatcac agtgaacaca 240
 ctggggagat gtgctttttt ggaaaactca aagggtgctag ctccctgatt caaagaaata 300
 tttctcatgt ttgttcattc tagtttatat tttcatttaa aatccttttag gttaagttaa 360
 agcttttttaa aagttagtta aaagaattga gacacaatac taatactgta ggaattgggtg 420
 aggccttgac ttaaaacttt ctttgtactg tgatttcctt ttgggtgtat tttgctaagt 480
 gaaacttggt aaattttttt ttaactaaat ttttttctta aaataaagac tttttcacia 540

118

wraaaaaaaaaa aaaaaaaaaa actcgagggg gggcccgtag ccaatcgctt gtgatgtntc 600
gtatac 606

<210> 199
<211> 373
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (251)
<223> n equals a,t,g, or c

<400> 199
catcttggag gtcaaataat agtaggaaaa gttagcagaga tactgaattt tctgatgagt 60
gtactactgc agaaagagta ctgatgaaat ctccatctcc agcattacac ccacctcaga 120
agtacaaaga tagaggaatt ttacatccta aacgaggtac tgaggaccga tcagatcagt 180
cttctctgaa atctacagac agcagtagtt acccaagtcc ttgtgctagt cttctctctc 240
catcctcagg naaaggggtc aaaatctcct tcrccaagac caaacatgcc tgttcgatac 300
ttcataatga agagtagcaa tttagagaaac cttgaaattt ctcaacagaa gggatatctgg 360
gctacaacty cta 373

<210> 200
<211> 3652
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (306)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1412)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1519)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2101)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2102)
<223> n equals a,t,g, or c

<400> 200

```

acgagctgat gtctcccgga ggaatctgca attgcataat ttagttgggt gcttgtctac 60
tgtctctctc ttggcaaga atgaaagctc tatgagcaaa cagaccttgt ctgccttatg 120
atccatttta ttactagagc ctaggactgt taaattcatt aataaagtct ttccatcact 180
ttttgttctt tatattcctt tactcaattg atattcagca tgtgcagaac agttcttttc 240
caaggctgca taaaagtttt ggaatgaggc acataaataa tatccttcta ccaataaatg 300
ctatcngtta taaaatagtt tttattttat aatcactgaa tatgtcaaaa ctttacagtt 360
caggcctttt gaatcaaagt caaaatcaaa tatgaaaagg ttaatgatct tgtccactaa 420
aattgtagtt tgccatacag gaaaatagac tcttaaaaaa gataaaaaaa aaaaaatcat 480
tcttaaggaa acatattaat aagacattta aaaaggctaa gatctttaat gtgaaaaata 540
ataagataaa gatgacaacc actgaagaga agaaaaaacg ttttatgttt tttctaaatg 600
tgtgtaaaaa caaaatcttg tacctaccaaa aatgacactt ttttcaaaga aaggatatcaa 660
atgtgtatac tttaacacac agcccttcct tgtgtaaata tataggaaat ccttaaagga 720
gcataaaaca atttacttag aaattctata cttaaactta ttcaaaggaa ataattaaag 780
gtgtgtaaat aagatatgca tagcattgct ctaaatgtca aatagtaggg aactaggtaa 840
ataagatata tctatttagg gaattagtca agtaagatat acctatttag ctaattccat 900
gtagccatca aaaggatacc atagaacaga acttattgat gtgaaaagat gattaaaatg 960
tacttgttac taaaaacagc aggctgcaat actgtattaa ataatgagcc catgctgtat 1020
atctagacaa acatatatca taatgataat aataaatgta tgagacttat atttttgctt 1080
ctctgtatth tctaatttgt ctgtgataaa caaatattat taatgtaatg aagaataagc 1140
taaaatatac aaaaacaata acaactataa aaagaacccc ttcaatcaaa aagagatcat 1200
cagggattta attcaactat ggattggcac tattaggagg ccaaatatga ttcgttgaa 1260
tgaactgtag taaagacaag atattaggaa aatgttttaa ttatgtgaga actattctca 1320
agcactttta agatctatth gcaagataac aatgtgctaa ctttaagtaa tgtctatgta 1380
ttcttgagac cagctttgac aatgacagct gncattccat ttgacttgga cttacattat 1440
gtttttgtcta ttttttcaaa aacagaaccc agggactgat tcttacaagc atttttctta 1500
agattcactg ggtggctgna aatctgatca agctgttctt tgggagatca ttattcaaca 1560
cttatcacat actttattth tacagctatg actgtcactc cccaagcttc acttcataat 1620
gaaaataaag aatacagccc ttttggaaaa gttggatggg aataccaagt gcgtaagttt 1680
ttagtacatg ccatatcaca accttctacg tggctgactt ttgacttttt catttctttt 1740
ataactgaca gaagacacaa aggcaaaaat gtcaacttca caaaaaatct tagtgctttt 1800
tggaaagaat gttatagatc atccagtcta acccctgat gttataaata tggaaattta 1860
ggcctagaaa ataggtaagt gatgaatcaa actagaagca ggtgtcctgc ctctaagccc 1920
aatccagttg ccatcatcat ttactattta catggaacat caggttctac tttagaagtt 1980
aactatcaac ctacagggtt aaggaaaata gcaatgtgta tatacagacc ttgcatctgg 2040
tagctgtatg gtgcctgtcc aggttgaggg gtactgaagc ttgtgccata gctgagaaat 2100
nntgtctgtc caggtgactg agactgtgac aatccacctt cagtcttgat gcctgcccac 2160
aatgcacctt aatcagttag tgatagctta tctatctgtc cattttcaaa agctggtaaa 2220
tatacaaaaa catacacttc cacaaccgtt taactacaaa tgcttcccca atcttatctc 2280
aaaaataaag ggtatacatg cattcagtga aataccataa agtacaactt cagtttttta 2340
aatccaggat tacagatttg aatgtctatt cacattatth tctcttgtht tattgcactt 2400
caagacatat ccttcttata aaatgtaact ccagtgatat attttcatac ttaattttgt 2460
tgttttaatt atgtaagagt tgaagatcat ctcttcaca gtaaagaaat agccataatt 2520
aaatttttagc taaatgttcc caaagttgct atattgacta gtgttaaaaa taaaatcctt 2580
ttttatatta aaaatattta ttagatccta taccatcaca gtatttttcc ctcccttact 2640
ctttctacta caaagctgat ttcagtacca actcattttg aagtccaaag aagcaatact 2700
gggcacagaa ctaaacacaa tgggtggaaag gcttttctctg aatatctagg tcctatcaga 2760
aaataagcac aaaggaagca gaacactaat gagctgaatc ttataaaaaca gcagtgattt 2820
ataaacaagt gaggttgacc agcagtttcc ttttgtccct gttagtgtga aatatttgac 2880
tataattgtt ttcgatgtag tctaaagtac ctttgttttt atcatatgat aatataaaaa 2940

```

120

```
tgatgtatct gtggccccc aatacttccc caaacaccag gctaacatcg taattttggg 3000
acttggattt ggcagcactg aggtatgggg ctgagctctg tctttaatta attacaatta 3060
aagacagtca tacatgttaa caactctcct tcattctcac agagggaggg aagaaaaatt 3120
tctgccgagg gaattcacat tttttaataa ttttgcttcg tacttaagat aaatgatatc 3180
tttaggatct agaatacaca gtagtcttac tgtttatttc cattttaggg gaatctcatc 3240
agcagagtac agctaggtaa ttgttttaag gcagtgggag aatctgactc ttggctgaga 3300
gtgcctactt taattcctgc agtatctcta aataacttca taatgacctt aacatttaag 3360
tcttaacaca accttaacat tttaaaaatg tgattttccc tgtaaagggtg atcccaaacc 3420
aatgaataac ccacacatag aaatgggtccc tggaaatata cctgccccag acaggtggca 3480
tgatggcttt agaaaatccc tttctttcca tgttgtcacc cctagggatt ttccacctct 3540
tgctgcattt gagactatac tgatctgctt ccagccttca cctataccaa taaaatacca 3600
ataattcatg tatttttttt ttttgagacg gagtctcgct ctgtcaccca gg 3652
```

<210> 201

<211> 551

<212> DNA

<213> Homo sapiens

<400> 201

```
gctgcagcga cgtcggggagc agaagcagcg ggcacacgac ggcgagcagc tgcagcagct 60
caagcacctg gagtcctttt acgaaaaacc tcctcctggg cttatcaagg aagatgagac 120
taagccagaa gattgcatac cagatgtacc aggcaatgaa cacgccaggg aatttytggc 180
tcatgcacca actaaaggac tttgggatgcc actggggaaa gaagtcaaag ttatgcagtg 240
ttggcggttg aaacctatgg tcaccgaacg ggtgacaaag aatgcccttt ctttatcaaa 300
ggcaacccaa agtttagagca gttcagagtg gcacatgaag atcccatgta tgacatcata 360
cgagacaata aacgacatga aaaggacgta aggatacagc agttaaaaca gttactggag 420
gattctacct cagatgaaga taggagcagc tccagttcct ctgaaggtaa agagaamcac 480
aagcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaagggggg g 551
```

<210> 202

<211> 665

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (463)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (582)

<223> n equals a,t,g, or c

<220>

121

<221> misc feature
 <222> (612)
 <223> n equals a,t,g, or c

<400> 202

```
gcggcacgag aagtcacagg tcttgccaat actggtgtag tttcttgccct atatccgtaa 60
tttgaaggaa atggtragag tgattagaga agtgtaatta ctgtaatttt ttccccattt 120
gtagtttctt gctgtatcc ataatttgaa ggaaatggta agagtgatta gtgaaatgta 180
attactgtaa ttttttcccc attcaacttt atatatcttt aactgatgac cagatcattg 240
ttgttctgaa ccagtttgtg gtcagcaagt gttttgtggg gttttgtttg tttgttttta 300
aagaacagtt tgggtcactt gacatggttc tccaaaggga tkttatgggt tgtwtttggt 360
tctgggtgat aaccgacttg ttagataatt tagataagca accgagttgc catgtttggt 420
tgtcaaactc caagtgtagc ttatatttta tgttcctaga gangttgtca nggaaagatt 480
tgaccctttg gcaaatctgt ttgaatagag atactaccat gctgccaat aaggctttct 540
ggccctgaaa aatatacgga attattcttg gaaatttgaa anggaaaaaa gaaataaact 600
gatccatggt tnttaccatg ccaaattaat tgaaggaatt ttcttaaaag gtatctcccc 660
tcggt
```

<210> 203
 <211> 2102
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (1861)
 <223> n equals a,t,g, or c

<400> 203

```
aaaaaaaaaa aaaaaagaaa aaaaccaaac taaccaaacc tctgtaaaag agtgctttga 60
gctctacaaa taccaagtat ttatttgggt atatttttag aatgtagcca tacagtgtaa 120
ttatgggtat ctgtcatgga tcacaattat tattcatagt aagtcattgt gatacagaag 180
tttgtttctt cacttccccct taagaagcca actatagtaa tcatgcaaag ttgaggagta 240
tgtccttcag ggatataaaa agaaaaacaa atctgttttt tgagctaaaa gagcacatcc 300
aaacaagaat ttaactggct aaaaatttagt aattactgtt aagtaactat caaacttgaa 360
atcttacaaag ataaatgggt aagatgtctt gagtatttgg gatggggggc tgtgagtctg 420
attgagacat acatttttaca gagtagcagc actggaaagg gctagtccaa cctcccagcc 480
tctgcttggg tctccgctgc cccagccaca cacatcctag aattcttgta aacatatctg 540
gctctgtgtt aacagtgcac ttgttatatg ttttctaaga gattagtctt tctgtgtatt 600
tttccaagta cgctgaaagt agtagtatga acttaaggag gctagtcaaa gaaacttgga 660
gttataggta tttttaaaga ataaatcctc aattccatca tcacttggcg gggagggggc 720
acttattaag cattttagat aataaaaactg gttaagctta ctctggtaga acagacaatc 780
aaatctgggg attgctgaga acaataataa gctgaagtat ggctcacaga atcctaacac 840
aatcatttaa gtctctagtt agatttgtta tcctaaaatt tttcatagaa ttttaaaatc 900
taattctgac ttgtatggtt aagaaaagca gttaaatatt ttactactta tcaagggtt 960
ttaaaataaa taaatctgat tgataggaag aaaggcaaat aaatacctat gtagacattc 1020
tataataaca aagagccata gatgataaag gaattagatt ttaatgtaga atgggtggtt 1080
tctgaaacaa aggtatgtgg tactttgtag ttattgatga gaagccagta accagtagtg 1140
ttttcctaga tatatgcccc cctcacaca actttcttca ttaacaaaca ttaaatatgc 1200
atttgatatc tattaaatta tattgtataa tgctgaagga aaacaaaaag tgttcaaata 1260
atcataactt ctacattaca ggttctgttt agatgcagaa ctagaggggc cagggtaaat 1320
```

122

```

gtagataaag agatatatag caccatgctt cttaatgctt catacttttg caaacagaaa 1380
aaaaaagttt tactttttatt ataaaaacttc atctatgggc aaagtaaaca ctgttacatt 1440
taaattgctt tttaaaaaca attgcatctt aaaaagtcaa aaatctgaaa tttaataata 1500
tgagacttac actgaatata atgttcattt agaagttgct gtgggtccact tcatttataa 1560
ggaacaaaata tttttacagt acactatagc aacagcaaaa gccctctctc accctgatag 1620
gaatgggttt gctgggtgct tagaagttag attcctgctg aatagaatta gccatcctta 1680
aaagatttta atccaatact gaactgttta taaaatgctt tctctattgt aatgtactgt 1740
aagtagtgaa attctgtata tactgctatt ttctgtctgt tcattgttgt gaacttctta 1800
tgtatattag tgaaataaat ttccagcttt catgttggtt cctaaacatt cataagtata 1860
nctaactatt aagagatttc ttcccttctt gagtaacaaa ttgggtgatt atattctttc 1920
tgatccaacc ccaaaaacta gctattctga aaaggctgat gttcactaat gggaagaatg 1980
aaatgaccct tcacctctta agggaaaaca gcctccgcca ttccctttca aaactatact 2040
tcttttactt gatactcaaa acttctgcac caaatcagt cagtattttt ccagaatgcc 2100
tt 2102

```

<210> 204

<211> 283

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (181)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (282)

<223> n equals a,t,g, or c

<400> 204

```

aactgatatt taataatatt taatattgct ctaaaatttc tggctaaaat gaaaatattc 60
aaccatcagg aaggagaaac aaaactatta ctgtttgtta acagtttatt atcagtactt 120
acctaaaaat cctggagaat gagctcagaa atattttctaa gagttgagac agtttagcaa 180
natgaacaga tacaacctca aaccaaacca aactagaaag ctacagaggac acagaatgcc 240
agtactgggc tgggcaacac ctctgttggt tgtgaaaatg tnc 283

```

<210> 205

<211> 425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (77)

<223> n equals a,t,g, or c

123

<220>
 <221> misc feature
 <222> (424)
 <223> n equals a,t,g, or c

<400> 205
 ccacaccccc ataaggccat ccaaataatatt aaangccccc ccagtgggaa atttggtggt 60
 taaaacctca atggaancct aatattttccc ttatgtccgt tagtcccctg taaaatgtta 120
 ggtcacccca aggaaagggg agaaatagca atggttgttc ctaagggtatt gcttgccctc 180
 catgtcttcc taaagagcag aacttggagt ttctccttta tgtagagaag aagtwactta 240
 ggggtgtatth gcaatgaaat attcatagat attgaaagct tgtgtttaca tkaaatatgt 300
 ttattatcaa gaagtccttt ttccaattct gtacattaaa tatatgtgtt ttaaaaaaaaa 360
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg 420
 gggnc 425

<210> 206
 <211> 483
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (444)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (469)
 <223> n equals a,t,g, or c

<400> 206
 cccacgcgtg grcagaccgc gcagggagca cacaccgcca gtctgtgcgc tgagtcggag 60
 ccagaggccg cggggacacc gggccatgca cgcccccaac tgaagctgca tctcaaagcc 120
 gaagattcca gcagcccagg ggatttcaaa gagctcagac tcagaggaac atctgcggag 180
 agacccccga agccctctcc agggcagtc tcatccagac gctccgctag tgcagacagg 240
 agcgcgcagt ggccccggct cgccgcgcya tggagcggat cccagcgcg caaccacccc 300
 ccgcctgcct gcccaaagca ccgggactgg agcacggaga cctaccaggg atgtaccctg 360
 cccacatgta ccaagtgtac aagtcaagac ggggaataaa gcggasgrrg gacagcaagg 420
 agacctacaa attgccgsam cggntcatcg agaaaagaga cktgacggnt taamgaktga 480
 tcg 483

<210> 207
 <211> 976
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (193)
 <223> n equals a,t,g, or c

124

<220>
 <221> misc feature
 <222> (929)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (958)
 <223> n equals a,t,g, or c

<400> 207
 agcttttcagc aagagatggt cacaatcaga aggataatac aaagtcaaaa gagaaggaga 60
 gtgaaaacgc ttccaggaga tggtaaagga aataagcata agaaacacag aaaaagaaga 120
 aaaggggagg aaagtgaggg ttttctgaac ccagagttat tagagacttc taggaaatca 180
 agagaacctc cangtgttga agaaaataaa acagactcat tgtttgttct cccaagtaga 240
 gatgatgcc aacctgttag agatgaacca atggatgcag aatcawtcac ttttaaatcm 300
 gtgtctgaaa aagacmagag agaaagggat aaacccaaaag caaaggggtga taaaacccaaa 360
 cggaagaatg atggatctgc tgtgtccaaa aaagaaaata ttgtaaaacc tgctaaagga 420
 ccccaagaaa aagtagatgg agaactgtgag agatctccct cgatctgaac ctcccaatta 480
 aaaaagccca aagaggagac tccgaagact gacaatacta aatcatcatc ttctctctcag 540
 aaggatgaaa aaatcactgg aacccccaga aaagctcact ctaaatacagc aaaagaacac 600
 caagaaacaa aaccagtcaa agaggaaaaa gtgaagaagg actattccaa agatgtcaaa 660
 tcagaaaagc taacaactaa ggaagaaaag gccaaagaag ctaatgagaa aaacaaacca 720
 cttgataata agggagaaaa aagaaaaaga aaaactgaag aaaaaggcgt agataaagat 780
 tttgagtctt cttcaatgaa aatctcgaaa ctagaagtga ctgaaatagt gaaaccatgc 840
 accaaagcgc aaaatggaac ctgatactga aaaaatggwt aggaccctg aaaaggacaa 900
 atttctttta gtgcgccacc aaaaaaatnc aaactcaaca grgaaactgg gaagaaantt 960
 gggagttmcc gaaatt 976

<210> 208
 <211> 660
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (560)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (567)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (583)
 <223> n equals a,t,g, or c

<220>

125

<221> misc feature
 <222> (589)
 <223> n equals a,t,g, or c

<400> 208
 ccacgcgtcc gccgacacgt cgggattggc ggctgcagcc aggggtcctc cgacgctggg 60
 cttccgtgag cggegtctctg ccaggtgggg ccggagctgc ggggagggag ttggcgccta 120
 gcgcgcactc catccccgcc tctgcagtgg actcggccgc agaatcgggg tcccgggctc 180
 ctggaacttg tccscgccag gccgcggcga ggaggtcact ccagccgatc tctggaccgg 240
 attcgtccca ttctcgtcct catggtggac aagaaactgg tgggtggtttt cggaggcaca 300
 ggtgcccagg gtggctccgt ggcccgcaca ctcttggaag atgggacatt caaggttcga 360
 gtggtgaccc gaaaccctag gaagaaggca gcaaaggagc tgaggctgca aggtgcagaa 420
 gtagtgacgg gagaccaaga tgaccaggtc atcatggagc tggccctgaa tggggcttac 480
 gscaccttya tcgtgaccaa ttatgggaga gctkcagcca ggagcaggag gtmaagcagg 540
 ggaagcttct tgctgatctn gccaaagngcc ttgggcttca ctntgtggnc ttcaaggggc 600
 cttgaggaca ataaagaagg ttacgggaag ggagatttgc cgccggggaa cttttaccgg 660

<210> 209
 <211> 514
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (56)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (464)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (467)
 <223> n equals a,t,g, or c

<400> 209
 tggaaccaat ctttgtggta catattccag ctttttgaat gagtgcatat ccagtnagta 60
 cctttaaagt aacactttgt acataacaar tactcagcaa atgtgaaact ttatttgctc 120
 ttacttcaaa attagtccaa aatggttgaa ataaaatata agacattgat ctagatatga 180
 ggtttttctc cttcattctc agctgtcgaa gaaatcraag tagcatatgc acaaggwtaa 240
 aaaccacata tacaaatact atagaacagc ttataatgaa aaccttgccct gcctttataa 300
 aaaatgtgat tatcttcttc tgtaaatgtc aataaaaagat ggtttgcctc agaaggctta 360
 taaatgggat tatgttcttg agggtttaca tatgaaaaat gtagaaaata caaaaagtgt 420
 ctatatatac aaaaatgtaa gtgttaacat ttttatattt gcctntcnagc ttttttttta 480
 aataaaaagga atgccatatt gccattaaaa aaaa 514

<210> 210
 <211> 173
 <212> DNA

126

<213> Homo sapiens

<400> 210

```

gtcaatgctc tgaaatctgt ggagcaaacc acagtttcat gcccatcgtc ctagaattaa 60
ttcccctaaa aatcttttgaa ataggggccc tattttaccct atagcacccc ctctaccccc 120
tctagagcca aaaaaaaaaa aaaaaaaaaa aaaaccctgg gggggggggc cgg 173

```

<210> 211

<211> 1521

<212> DNA

<213> Homo sapiens

<400> 211

```

gctatcaaaa tcatgacatt atgtcacttg gagcaacaca gttgaccgcg caaggcagcc 60
tcttcctcca tagatggatg aacgctgtgg ccgctgctcc tkcmctggcc atgccctgay 120
gctgccaaaca ccaactgctcc tctatttata agtcttarta gaggttgctga cccagcaata 180
actgaacagc tgatatgtac ctcacactaa gccaggcgct tcatatgtat ctaacttgaa 240
aaatgctgag ctagttacct taacaccatt aacttttact taaaagtttg tttttctttt 300
ttaatcccag tgagctccaa acaagtttta ggaggctccc caaaaccagt gaagacttta 360
actaaaagta gaatttcaaa gtattagaaa ccaaacccca aaattaaatg tgaagatcag 420
tgtctgtact gagctggccc atctggtgga cacaggattt gcgttatcga ctgcaatggt 480
accaggatt cagattttct agcatctgtc agggttaaga aaattggatt gagtaccaa 540
tacagcagag caaaccgggc tttgaggcaa gggccccatc aagtagtcat gcagtacttt 600
tgtaggggtt ctgggtgcaa atcttcctcg tccctccac cttctcctgg cctccttgta 660
aacccaaacc gccagggtacc tcaattttct tcaagaccag gctgttctta atgttggtta 720
attggtcaag gaaatgggtg agccactgct tgctctgcac atcgctcctc gagtgtcctg 780
tcttcaggca gtacagcagc tgcattggct tggcctgcag gagtaagtgg cccattccta 840
ggctgtcccc aaagatgtgt cctctgaaga agctggctcag gtagaggggg tgccactat 900
ggttatagat ggtgaaggag atgctgccc ggtcgagcgt tttgtccacc tgccagggtg 960
acaggagtgg gttgggggca ccacgcagag catcttgtac ctgcgcgaca cctgctggta 1020
ctggagctgg cttgcgtttc cctgtgccac acgcagatcc tgcactgtac tgccagtc 1080
actgacttca gcaaatgtgt ctgggttcag cagcgagttg ctgtgtgagg ccaccagaat 1140
ggagggtgata tcggcctcag tgctcactct ggagggtggag aagtggctcag agtcctctgt 1200
ggtgaaatgg ccctacacca aagtgggaga cattcagaat cgaggcgaaa ttggcctcag 1260
tgctcctctt ggaggcagag aagcagtagg agtcggtggt gaaatggccc tgtgtgaatg 1320
tggaagacca gcagattgga ggtggaattg gcctcagtgc ttgtcctgga ggtggagaag 1380
cggtcagagt ccttggtggt gaagtggccc tgcacaaaac gttgtctccc cttggccggt 1440
gaaagaataa aagaaagctg gccacttgca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa aaaaaactcg a 1521

```

<210> 212

<211> 1875

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1052)

<223> n equals a,t,g, or c

<220>

<221> misc feature
 <222> (1291)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1849)
 <223> n equals a,t,g, or c

<400> 212
 gtctgtctgtt gtcagaaggc agggaggggtg atgaaggact gacccacatg gactgggatg 60
 tgtgtcgggtt atgggcatga ctgcacgttc actctcagtg ggatctgggc aacatggagt 120
 tcattgtcct gttgcttact tactgcaatg tctttggccc tccttttcaa ctggttcctc 180
 tgttggggccc aaagggttggg agtaggagac agtatcccag gctgacaagg gcttgccytt 240
 taccttgggc accttggttaa tttttagcct gtgcccttcc ccacctttgc cctcccagtg 300
 gttgggtatgt gggaaagcca tctcagttcc tgtgacttca tgtctcaaac caaggatgag 360
 cgtctgggtct ctgctatgat ggtgggtatcc gaggccttcc cctgcccagt ctgggtgctg 420
 cccacacattg taccggacac tggattcctg gacccccctc tcctttcctt tctttccttc 480
 aggtcacgca gccctgtact gtatccagca ccacagaaac ctcaagtgtt ttctctgtct 540
 gggttggggc acaaggaagc cttaggggtat ggggaaaggc tgttattacc tagagtttac 600
 tcccaggcca gggggctgcc atcttcttca cagacatccc tgaaaggaag cccctttggg 660
 gcagggaggt gaggacttca tctcaacatc ggctgggtggg ttgtagggga gcttttyctt 720
 ttctttcctt tttttttgtt tttgtttttg tttttgtttt tggtaacatg ttaggagtta 780
 atgttgcaaa gagtagttta catcttcact ttctgaagac acttgaattt aggaccgatg 840
 tatctgtgac aagcatgcca gaagtggcag gggccatcag ggctaaccac ttcacacctt 900
 ccatcgctcc atggggatcc aagacctgag ataaagcaac agcctgccc gatccctctg 960
 ttcaccttat ccttccaag gttgggtccat gccaacataa cctctgggca tcagacatca 1020
 gcaggtctgt gtgcctcagc cctgttaagg gncagggtttc tctttagccc tcttctgca 1080
 cttgggagca aaggcactac cagtagagaa gggccatcca gccgtgcccc agcctggacc 1140
 cctggggctc agatagaggt gctgagcccc tgtgtcaaaag ttgttaaag tttttgtttt 1200
 gttccattgt agctcttttt tttttttttt tccctttcct ggtgattgat tttacaaaag 1260
 aaagtaagct gcttagaagg ccctggaagg naagttagga ggagggacaa ggaagatgac 1320
 tagttacgga gggtaggggt tgttttttgc caaaaagcct gggtagagtg atctgaatta 1380
 tctggcacc tcctgaatgg aacccagag tacctcctgt gtggaagggc ccctggattt 1440
 tccctaacac ccacctctc ccccttcagc catgctgatg gcagagaaga taagaacttg 1500
 gagcccattt ctactggag aggaaaactt gtcactctggc tttgaggaga aggttccacc 1560
 ttacgtctgt agtacattat ctttactatg tgctaggata tcatatttaa aaggacaaaa 1620
 aaatgtaaaa tacttgaatg agcttgattt ataacattaa tattattgag agtatctgct 1680
 ttccaggctg aagtgattca ttcattatcc tagtctgct ttagtccttt gtaatttgtg 1740
 gtaattatgc ttttcttttt aatacaaaaa aatgtataaa aataaacact tgaaaaggca 1800
 aaaaaaaaaa aaaaaaaaaa aaaactcgag gggggggccc tacccaatnc gccggatagt 1860
 gatcgataa caatc 1875

<210> 213
 <211> 1917
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (798)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (802)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1073)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1748)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1887)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1891)

<223> n equals a,t,g, or c

<400> 213

```
gaattcggca cgaggcagtg gtgtgatctc agctcactgc aacctccacg tcttggggttc 60
atgcaattgt cctgcctcag cctcccaagt agctgggatt acagacatgt gccaccatgc 120
ccggctaatt tttgtatttt tagtagagac ggggtttcac tatgttgggc aggctgatct 180
caaactcctg acctcaagtg atccaccccc ctccggcctcc caaagtgcta ggattacagg 240
catgagccac catgtctggc cctacttttc ttttatgcct tctttttgga ttaatcaaat 300
atttagtttc attaccccac tattaacttt ttctattata tattcttttt ttaattaagt 360
gattaccctt gggttgttac atacatcctg aacttccttat agtaaataata catgattaat 420
ttaacctctt ccctagcaat gctcagattt tagaacatta taattccatt tagtctcttc 480
taccttttgt tttattgttt tcatgtattg taatcctaaa catattttac accccacaag 540
acaatatatt agtgttgcat atcctcaata ttcatctaga ttaatccata caattactct 600
ttctattgtc ttctactcct tactgaattt ctaggctttt atctgaaatt attttccttc 660
tgcctgaaga actacctttt atagtaattt tagtgtaatt ctgcttarga agtattatct 720
gttcttggtt ttctgacaac attttcattt ctcccttcatt tttgcaggat gtttttgctg 780
gggtgtatttt ctgggtcngt antyctagat tacagttact ttcttcacta cttatattct 840
cactgccacc attttattga aagtcagcac caaatcaatt aaaaactgaa ggtaatatatt 900
ctccccctca ggctgttawa aatttttttc yttgaccttg gtttttawta gkgttactgt 960
aatgtgccaa gatgtgmctt tctttawatt catcctgctt gggattttca ggaattcatg 1020
cctcagggct ttatgtcttt cattagtttt gggaaaattt taagccatta acntttcaaa 1080
```

129

```

gatcatctct tccctattct ctcttyctct ctctgctatc cttttgraac tccaattmca 1140
tgaaagtttag atttgttcat gttattcctt acgtttctta tgttcttttt tatattttcc 1200
atctttttcc ctctctgagt gtcagctctg tgataaggta gtcttgagga cttgtgtctg 1260
ctggaaggaa ctgatctgac ttggagamcc tcaaaaaagc tctatctctg gatattcatg 1320
aaaagaatag caattagaag caatctgctc aaagtcagca ttgcaactgc ttagggctgc 1380
aatatagggtt gaggcaccaa gagactagca aatattttat agggttacct gagaaacaag 1440
agagccacaa gggactttga taagctctat aatatgtctg taatgttcct gggaatttag 1500
aaggttgtgt gcatgttcaa ggctgcatgc atgttcagga aataccaaca ggggccaagt 1560
tacttattca tctcttactg accttggagc tcagtgttaag caggcaatga aacctaaggc 1620
aaatttataa actgcctgaa ctttgaaggc atgtggaaac tcataaacag cttctctcag 1680
ccagttgcag aagatttact tattcaagtc atttaagaaa accttctaac ccaaaatttc 1740
ccatgctncc tgagatgacc aggacctaga agtagctaaa atagaacaga tttaaaaagt 1800
acataattct gtggagatct gaggctttna ctagcttgaa tgtacaacac acaacctgtg 1860
ggtgggataa attaagcata aacttgncta naaaaaaaaa actcaggggc cggccat 1917

```

<210> 214

<211> 1544

<212> DNA

<213> Homo sapiens

<400> 214

```

ggcacgagct atagcaatct gggttttctt agccaattga aatgggcatt tattagatca 60
tttaagcatc atatcaatat agtatatttg gcgactttat gataagttct tatgatagat 120
gttcaaaact ctgctcaggt gacattttta tggatccaca tagtttttgt catatatgaa 180
aagaaagcat tgagttgtgc agatgggttaa atgtgcattg agttatttct ctggaatttg 240
catgagaatg gaccgacttg tagttgtatt aacttttcta gtgccagggt tagaaagttt 300
gatctgtgta gttttttaaag gcagcatcca aatcacttat attcagaaga aaatggtaac 360
agatttagaa gctgtctata ttttcccat tatccataat acatattatt ggcaatatgg 420
ttttcactct ttgttggttaa cgtatcaaca atgtgcaata gccactaata atcatttgtt 480
aatgcatgct tccaagttct gtatttgaaa atctcagact tcatatatgg taagtgatgg 540
agtaatttat aacttttatg ttgaattctt gctactttta aaaattgtgc ttctcctttt 600
ttaaagcata tgacttactt aacagctgat agtcagttac ctggattttt agtatttttt 660
tacatcacia aaagatttct ctgaagtttg cgcaggggtc tatttgtagg cagtttccaa 720
cttactaata agtaagggtc tgaaagttat aagttagctg tctggaatag atagtctcat 780
agaaaccagg ttgtagatgg tgatttgggt ccttgggcaa cctactgaaa cccatttact 840
atataatgtg gctgaataat attattgata gtgctatagt atttagcaac tgtctgtcaa 900
gtgattttga actctcattt tgaaatctaa ctttcatagc attatactga tgaatttttg 960
gtagtgcgat ttgacttttt ctacctccat tctaccagtt cacagcgcac tctagcagtg 1020
gaaatcaaaa aacctattga gatggaattt gggaggaaag gaggacttac tgatatccct 1080
agctgtagaa agaaagtaac tgggtatcct gtctgaaaga ggaaggatgt gatgatcttc 1140
atggctctgt tgtggagatg tatgtctgct tatacatggc aggcaaccaa ttggagggtt 1200
atatatttta aaaaataaag aaggggcggc cgggcgcgct gctcacgcct gtaateccaa 1260
cactttggga ggccgagggc ggcagatcac ggggtcagga gatcgagacc atcctggcta 1320
acacggtgaa accctgtctc cactaaaaat acaaaaaatt agccgggcat ggtagcgggc 1380
gcctgtaatc ccagctactc aggaggcgga ggcaggagaa tggcgcgaa cccggagggc 1440
gagcttgcag tgagccgaga tggctccact gcactccagc ctgggcgaca cagcgagact 1500
ccgtctcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1544

```

<210> 215

<211> 1762

<212> DNA

130

<213> Homo sapiens

<400> 215

```

catgagccac tgcacccagc cgatactact atatccccat ttacacagatg agcacatggg 60
caaattgagg gtaaggcact gacccatgat catacagctg agaagtggca aaggcaggat 120
ttgaacctag aacctctggc tccacacact agtaatctaa accactctcc ctacaataca 180
acatacgtgg taaagatgtg tgggtgggcac gcaatcaacg taggtccctt cacagttgct 240
gggagaggca ggaatttgca gttcctccgc gttctcctcc tccgctgccc acctgtcctg 300
ggtcattcct gcagcctgcc ctgccctgcc tgggtctcacc ctccctctgc caacagaagt 360
ctgggcaggg ttttatgggc tctgataagg ccctggcagg gccgaagttc atgagcactt 420
cctcttttgca ggagggcgta ggggagggga cccaggtgat ttgggtcctg gctggtcacc 480
agggaagctg gcaagggaag ggagactagg gtgcgctcta ggagaagccg acagcctgag 540
agtcccagaa gaggagccct gtggaccctc ccctgccagc cactccctta ccctgggtat 600
aagagccacc accgcctgcc atccgccacc atctcccact cctgcagctc ttctcacagg 660
accagccact agcgcagcct cgagcgatgg cctatgtccc cgcaccgggc taccagccca 720
cctacaaccc gacgctgcct tactaccagc ccatcccggg cgggctcaac gtgggaatgt 780
ctgtttacat ccaaggagtg gtcagcgagc acatgaagcg gttcttcgtg aactttgtgg 840
ttgggcagga tccgggctca gacgtgcct tccacttcaa tccgcggttt gacggctggg 900
acaaggtggg cttcaacacg ttgcagggcg ggaagtgggg cagcgaggag aggaagagga 960
gcatgccctt caaaaagggt gccgcctttg agctggctct catagtcttg gctgagcact 1020
acaaggtggg ggtaaattga aatcccttct atgagtacgg gcaccggctt cccctacaga 1080
tggtcaccca cctgcaagtg gatggggatc tgcaacttca atcaatcaac ttcacgag 1140
gccagccctt ccggccccag ggacccccga tgatgccacc ttaccctggg cccggacatt 1200
gccatcaaca gctgaacagc ctgcccacca tgggaaggacc cccaaccttc aaccgcctg 1260
tgccatattt cgggaggctg caaggagggc tcacagctcg aagaaccatc atcatcaagg 1320
gctatgtgcc tcccacaggc aagagctttg ctatcaactt caaggtgggc tcctcagggg 1380
acatagctct gcacattaat ccccgcatgg gcaacggtac cgtgggtccgg aacagccttc 1440
tgaatggctc gtggggatcc gaggagaaga agatcaccca caaccattt ggtcccgga 1500
agtctcttga tctgtccatt cgctgtggct tggatcgctt caaggtttac gccaatggcc 1560
agcacctctt tgactttgcc catcgctctt cggccttcca gaggggtggc acattggaaa 1620
tcagggtgta tgtcaccttg tcctatgtcc agatctaatc tatctctggg gccataactc 1680
atgggaaaac agaattatcc cctaggactc ctttctaagc ccctaataaa atgtctgagg 1740
gtgtctcatg aaaaaaaaaa aa 1762

```

<210> 216

<211> 253

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (238)

<223> n equals a,t,g, or c

<400> 216

```

gggtaaata ga gtgccagggc cggcaagccc ccgctccccg ggctctcggg gtcgcgcgag 60

```


131

```

gatgcttggc acgtaccccg tgtacatact tcccgggccc ccagcatgga aataaagcac 120
ccascrcctgc cctggggcccc tgcgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagggg ggccgntnta 240
aaagggtccc tcg                                     253

```

```

<210> 217
<211> 511
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

```

```

<400> 217
ccccagcggg cgcgggccgg agcacgggya cccagcatgg gggtaactgct cacacagagg 60
acgctgctca gtctggtsct tgcactcctg tttccaagca tggcgagcat ggcggtata 120
ggcagctgct cgaaagagta ccgctgtctc cttggccagc tccagaagca gacagatctc 180
atgcaggaca ccagcagact cctggacccc tatgtaagca cctgggcccct tgtggcatct 240
gagtctcaga gaactatggg gttaggaagg gagtgagaag cagggaggac aggcctagcc 300
ccactccata tggccaggtc ggggaactga gtcgctatgt tattccagcc ttaaccctga 360
ggagctaagg ctggccctcc agctttccta gctctgtggt cccggggcgg gactccggac 420
accatcacca tgctmactgc ttactcagtg tgtttcctgc acacctgcca ngcttctggt 480
ctaggcaatg ggacgtagca gtgaagcaag a                                     511

```

```

<210> 218
<211> 2945
<212> DNA
<213> Homo sapiens

```

```

<400> 218
ggaattccaa ctatggcctg ctgcctgttt ttggetgggt agctaagaat gattttttaca 60
ttttttaaat attggaaata tcaacaccgg aatttatatt catgatatgt gaaaattaca 120
tgaagttcaa atctcagttg ctagaaataa agttttattc gcacacagcc tgctcatttg 180
tttacctatt gtgcatggcc actttcacat tacagtggca gagttgaaca gctgctgcag 240
agactagcca caaaactaat aacgtttact gcttggccct tacagaactt tgccgagccc 300
tcattttaag taatagattt aaacagttct cataagcagc tgctggcttt gaaggtaggt 360
gcagccacta gtgcttttct tggcagattc attgccaagg aacagtttgt taagtaattc 420
ccttgttttt tggtgccaggc tccataaaga aagggttctc acgctcaaat atatgggcaa 480
tacctcatgc tatgtatgta tatgtgattt atttctctct aggggaacaaa cctgtataat 540
tgcttaaatgt agtctcctta aaaggtagaa aagggtctct tgggtcaaata attgtaggaa 600
aaagattgac aatcacagtg ctgagaaggc ctccaataga gaagttgggt tagttgttcc 660
tcgatctccc acctcctcct tttgagctca gcctttttag aattaatcat tgccctcctc 720
tcttgccccct gagtggaagg gatgaggccc atgggctttg tatccctagg aggagaaaga 780
gccagtaagt gaggagcttt taaagccctt tctttgtggg agggggccaca agggggccagg 840
tctcttaggg ctgagaaagc caaggccagc atttctcaga gtgctgtcag gactgtctgc 900
ctcagaatca tctaaggggc cagctaaaac agactctggg gccatttcag actcactggg 960
cagtagagct caggaatctg catgatgttg ctgacgaaag cttagggttg atttcctctt 1020
gggtgtcccc cccaagagct tgaagatcct gtctccttcc tcctctgtcc caacctgggt 1080
tggatatatt ttgaatgaat aataacacct gccacttata agtgtttatt ggggtgctgag 1140

```

```

ctgatctcat tggatttttt ttttttcttg agacagagtc ttgctctgtc acccagtcac 1200
ccaggctgga ttgcagtggg gtgatctctg ctcaactgcac cctctgcctc ctgggttcaa 1260
gtgattcctt ctgcctcagc ctcccgaata ggtgggggcta cagacacacg ccaccatacc 1320
tggccaattt ttgtattttt atagagacgg ggtttcgcca tgttgccag actggtctcg 1380
aactcctgac ttcagctgat ccacatgcct aggcctcaca aagtgctgga attataggtg 1440
tgagccaccg tgcccggcct gatctcattt ggatctttgc agcaatttga tgaattgggt 1500
gttctcgtta tccccagggtg acaggcaact gaggcccaga agaagggttg taatatgtta 1560
atgagttaag acatagcgcc agggttcatg tgggtgaggg tctgacacca gacagatgaa 1620
gggtcgtcgg ctacagtgc ttgagtacc gagctggggc agatttgga ccatggtgt 1680
gaggaacctc caccctcta atgctggcag aaaggagttt ggggagggca ggggctggag 1740
gaggatggtc ttcgccttgt tcaaggcagg cagcagcctt ttccctctca cgggtggcaa 1800
gtttctctgc tgcccagtc cctgggcctc ggagcactaa ggctggccac ctgctaggtg 1860
ggaaggcccc aaacggcttc tcactctgcc tgccctcact cctaccagaa tgacctcacc 1920
tggcagggag ggtggcccca gggcctgtc agctctgttc ctgccagcca ggagggtcct 1980
ggagtccctc ccaagcctgc cgcaagccca gagggcacat ccaagaggca agtgtaagct 2040
cctgtttcct tcactctcag cagcacaag ctctggaggc tggaaggcag caggcagggc 2100
cagaaggtat tttcatctt cctggaactg cgttaaaggg ccctgggcag tgaaggagcc 2160
agagccattt cctgcgtgct tacagcatgc cagggtgcctg gccacacact gcccacagga 2220
tcagcttgaa cctcagcag cccgcctgg tagggccagc cgtcctccca ttccacagat 2280
ggagccgtag gggctctcct caaaagtcac acagttagga gatagccaaa ttcaaatecgt 2340
ggtgcatcca tccccgtcca gggctcgttt cttacctacc ttgccccct gctaactcgg 2400
acacctcttg agtttgcat ccaagagcag aacctggatc ccgggggagg gaggcacagg 2460
gaggcgtgaa ggatgggaac cagcctcccc tgggctgctt gggcgggctt ccccttgcc 2520
agttctgctg cccttaactg cggccttggg cagggggcgt aacctttgca ggtgacgctt 2580
gggtctccct gttggaagac cggcaagatg ccgtgtactt actttaagaa gcaaataag 2640
gttgggcgcg gtgctcacgc ctgtaatcct agcactttgg gaggccgagg tgggcggatt 2700
acttgaggtc aggagttcaa gacctgccc accaactatg tgaaaccctg tctccactaa 2760
aaacacgaaa attagctgga tgtggtagta ggctcctgta gtcgcagcta ctcgagggc 2820
tgaggcagga gaatcacttg aaccgtggg ggcagaggtt gcagtgagcc aagatcgtgc 2880
cactgcactc cagcctggat gacagagtga tactccatct caaaaaaaaaa 2940
aaaaa 2945

```

<210> 219

<211> 445

<212> DNA

<213> Homo sapiens

<400> 219

```

ggtaccgggt ccggaattcc cgggtcgacc cagcggtccg ggaactgtga cttccccacc 60
ccaaattcta tggccggcta atgttttgc atggtgacta tcacccatct acctggaagc 120
accagaatgg cttagtacag ctaggagct cagccagatc tcggtgtctg ctgtttgaga 180
ttgtgtggaa ggactattgc taagaagcag gagacagact gaaccagtg ttggccacaa 240
gtgaggactg agaccagggt cacctcttgg ctgaacatgt tagcttgttg gtaaatggct 300
ctgcagtggg tctgcatttt agtggggaat ttgttttggg tcatcttggc attcccgcaa 360
ccatcttgtt ggttttttgg taaaatgtgg caccocytc agacctytta gctgtggaam 420
tgagrtatct tagcagggtc ccgtt 445

```

<210> 220

<211> 522

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (402)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (417)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (482)
<223> n equals a,t,g, or c

<400> 220
ccttttaaata atgaataata gtgatagaaa atgtcatttc ttggacaaat gaaaaattga 60
aattaatgta tataaattaga tattattagc tactcttagg tagcttcatt tgttgaaagt 120
ttgacaagtg aatgaagttc acatctggaa atcggtgaac atttttcgtt catggaactc 180
aatggctacg ttagtcgttt atgcttttca ctggttggtt aggggctttg gaagtaaattg 240
ccatcaacaa tggatacaga agacctggat ttggaataag ggcaaaattt atttgatggg 300
gctgaattgc tctgccagga gcatttggtt tgagatgaaa tggctctctt gagactgagc 360
tgccacctgg gcaatattgg ccgctaaggg tctctttatt cnccttactt ggacttnott 420
tcctggaggg aatctcccga aaaaggaaac tttccttccc cagggggggc ccaatgggtn 480
cnagggctgg cttcaaaatg gggtcccaa ctggtggcat ca 522

<210> 221
<211> 1516
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1493)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1497)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1508)
<223> n equals a,t,g, or c

134

<220>
 <221> misc feature
 <222> (1509)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1516)
 <223> n equals a,t,g, or c

<400> 221
 gaatgagcag gataactgtg tccctgattca tgatgtggac caaaggaaca gcgataaaga 60
 tatcttttggg gatgcctgtg ataactgcct gagtgtctta rataacgacc agaaagacac 120
 cgatgggggat ggaagaggag atgcctgtga tgatgacatg gatggagatg gaataaaaaa 180
 cattctggac aactgccc aaatttccaa tcgtgaccaa cgggacaagg atggtgatgg 240
 tgtgggggat gcctgtgaca gttgtcctga tgtcagcaac cctaaccagt ctgatgtgga 300
 taatgatctg gttggggact cctgtgacac caatcaggac agtgatggag atgggcacca 360
 ggacagcaca gacaactgcc ccaccgtcat taacagtgcc cagctggaca ccgataagga 420
 tgggaattggg gacgagtgtg atgatgatga tgacaatgat ggtatcccag acctggtgcc 480
 ccctggacca gacaactgcc ggctgggtccc caaccaggcc caggaggata gcaacagcga 540
 cggagtggga gacatctgtg agtctgactt tgaccaggac cagggtcatcg atcggatcga 600
 cgtctgcccaga gagaacgcag aggtcacccct gaccgacttc agggccttacc agaccgtggt 660
 cctggatcct gaaggggatg cccagatcga tcccactgg gtggtcctga accagggcat 720
 ggagattgta cagaccatga acagtgatcc tggcctggca gtgggggtaca cagcttttaa 780
 tggagttgac ttcgaaggga ccttccatgt gaataaccag acagatgatg actatgcagg 840
 ctttatcttt ggctaccaag atagctccag cttctacgtg gtcattgtgga agcagacgga 900
 gcagacatat tggcaagcca ccccatcccg agcagttgca gaacctggca ttcagctcaa 960
 ggctgtgaag tctaagacag gtccaggggga gcatctccgg aactccctgt ggcacacggg 1020
 ggacaccagt gaccagggtca ggctgctgtg gaaggactcc aggaatgtgg gctggaagga 1080
 caaggtgtcc taccgctggt tcctacagca caggccccag gtggggtaca tcagggtacg 1140
 attttatgaa ggctctgagt tgggtggctga ctctggcgtc accatagaca ccacaatgcg 1200
 tggaggccga cttggcggtt tctgcttctc tcaagaaaac atcatctggt ccaacctcaa 1260
 gtatcgctgc aatgacacca tccctgagga cttccaagag tttcaaacc agaatttcga 1320
 ccgcttcgat aattaaacca aggaagcaat ctgtaactgc ttttcggaac actaaaacca 1380
 tatatatatt aacttcaatt ttcttttagct tttaccaacc caaatatata aaaacgtttt 1440
 atgtgaatgt ggcaataaag gagaagagat cattttttaa aaaaaaaaaa aanttcnggg 1500
 gggcccgnnc caattn 1516

<210> 222
 <211> 1387
 <212> DNA
 <213> Homo sapiens

<400> 222
 acagttggct atgttgggtgc cgacctgaca gcactctgta gggagggtgc catgcatgcc 60
 ctcccttcata gtgagaagtt ccaggtttga ccataagcac ctctcactta ggtggaccag 120
 tcagctgctg tcgtcccagg gtggagccca ctgctacttc aggagggggc tgctcagggtg 180
 tagttaccac aggtgatggc tgagttcaga aacaaccagg ggggaagtggg aggaagaaaag 240
 gcaaaaagca tgaaggggaca gacaactggg aagaaccagg acaatcctgt gattgatgaa 300
 atagacttcc ttgaagcttt taaaaatatt cagccctcat cgtttcgaag cgctcattgga 360

135

```

ttaatggata tcaagcctgt tgactgggag gagattggtg gccttgaaga tgtaaaactg 420
aagttaaaac agagcattga gtggcctctg aaattccctt ggggaatttgt tagaatgggc 480
ctgacacaac caaagggagt tctcctctat gggcccccctg gatgtgctaa aaccactctg 540
gtgagggccc tggccacaag ctgtcactgc tctttcgttt cagtgaagtgg agctgatctg 600
ttttcaccgt ttgttggaga ttcagaaaaa gtgttgtctc agatatttcg acaagcaaga 660
gcaagcactc cagcaatttt gtttttggat gaaattgatt caatcctggg agctcgctca 720
gccagcaaga caggatgtga tgttcaagaa cgagttcttt ctgttctcct gaatgaatta 780
gatggtgttg gacttaagac aatagagaga agaggaagta aatcaagtca acaggagtgt 840
caagaagttt ttaaccgaag tgtcatgatt attgcagcaa caawtagacc tgatgtgtta 900
gatactgctt tgttacgacc tggaagatta gataagatca tctatatccc acctccagat 960
cacaagggca ggctttctat tttaaaagtc tgtacaaaaa ccatgccaat agggcctgat 1020
gtctccttag aaaacctcgc agcagaaacc tgtttttttt ctggagctga tcttagaaac 1080
ctctgcacag aagctgcttt gctggctctg caagaaaatg gactagacgc aactacagtg 1140
aaacaagagc actttctaaa atcacttaag actgtaaaac cgtcgtaaag ttgcaaggac 1200
ttggctttat atgaaaactt atttaagaaa gaaggatttt ctaacgtgga aggtatttaa 1260
aaatcacctt aaactcttgt tcagttcaca ttaattgaaa tgtgaacttg cctgtcgttt 1320
gcaacttcac acttttagaa tttgtgttta tatttctctg aagtgaataa ataaaaacaa 1380
acaaaac 1387

```

<210> 223

<211> 1506

<212> DNA

<213> Homo sapiens

<400> 223

```

gaattcggca caggtgggta gaggtgatgc agtgetgaag acctggggccc ctgctcagtg 60
cctttgtctt agaatgggtc cagcttggct ttggctactg ggaacaggga tcttggcctc 120
tgtccactgt cagccccctt ttgccatgg agataaaaagt ctgcaggggc ctcaaccccc 180
caggcatcag ctctcagagc cagccccgc ctaccacaga atcacacca ccattacca 240
ttttgtcttg cgtttgtata aagagctggc agcagacgcc cccggaaaca tcttcttctc 300
gccagtgaac atctccacca ccctggccct gctctctctt gggggcccaag ctaacacctc 360
agctctgatc ctggaggggc tgggattcaa cctcacagaa acccctgaag ccgacatcca 420
ccagggtctt cggagcctcc tccacaccct tgccctgccc agccccaac tcgaactaaa 480
agtaggaaac tccctgttcc tagacaagcg actaaagcct cggcagcact atttggacag 540
catcaaggag ctttatggag cttttgtctt ttctgccaac ttcacagatt ctgttacaac 600
tgggaggcag attaatgact atttgagaag gcaaacatac gggcaagtcg tggactgcct 660
cccggagttc agccaggaca cgttcattgg tcttgccaat tacatcttct tcaaagccaa 720
gtggaagcac cttttcagtc gctaccagac ccagaagcag gaaagtctt ttgtggatga 780
gaggacttct ctccaggctc ccatgatgca caaaaggaa atgcacagat tctctatga 840
ccaggatttg gcttgacccg tcctccagat agaatacaga ggaaatgcct tggcgctgct 900
ggtcctccct gacccgggga aaatgaagca ggtggaggct gctctgcagc cacagacct 960
gagaaaatgg ggccaattgc tcctgccag tctgttggat ttgcacttgc caaggttttc 1020
aatctctgga acatataacc tggaagacat acttcccca atttggctct ccaacatact 1080
caacttagaa gctgacttct caggagtac tgggcagctc aacaaaacca tctccaagg 1140
gtcacacaag gcgatggtgg acatgagtga gaaggggacc gagggccggg ctgcttcagg 1200
cctcctctcc cagcccccat ctctgaacac catgtcagac ccacatgcc acttcaacag 1260
gcctttcctc ttgtctcttt gggagggtcac caccagagc ttactcttcc tgggaaaagt 1320
tgtcaaccca gttgcagggt aaccatggtg ggaggccagg agttatctta tctcatcctg 1380
gaccaaacag ataggccaga accagcctgc atcctggggc tgctatgtgg ttcagttaat 1440
cagtgtgcca agattctaat aaagttgacc ttgggttctg tgaaaaaaaa aaaaaaaaaa 1500
aaaaaa 1506

```

136

<210> 224
 <211> 896
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (18)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (40)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (45)
 <223> n equals a,t,g, or c

<400> 224
 aaaagctcgg cccttaancc ttactaaagg gaacaaaagn tgganctcca ccgcggtggc 60
 ggccgctcta caactagtgg atccccggg ctgcaggaat tcggcacgag aagagcactg 120
 gccaaagtcag cttcttctga gagagtctct agaagacatg atgctacact cagctttggg 180
 tctctgcctc ttactcgtca cagtttcttc caaccttgcc attgcaataa aaaaggaaaa 240
 gaggcctcct cagacactct caagaggatg gggagatgac atcacttggg taaaaactta 300
 tgaagaaggt ctcttttatg ctcaaaaaag taagaagcca ttaatggta ttcacacct 360
 ggaggattgt caatactctc aagcactaaa gaaagtattt gcccaaatg aagaaatata 420
 agaaatggct cagaataagt tcatcatgct aaaccttatg catgaaacca ctgataagaa 480
 tttatcacct gatgggcaat atgtgcctag aaatcatggt tgtagaccct tctttaacag 540
 ttagagctga catagctgga agatactcta acagattgta cacatatgag cctcgggatt 600
 tacccttatt gatagaaaac atgaagaaag cattaagact tattcagtca gagctataag 660
 agatgataga aaaaagcctt cacttcaaag aagtcaaatt tcatgaagaa aacctctggc 720
 acattgacaa atactaaatg tgcaagtata tagattttgt aatattacta tttagttttt 780
 ttaatgtgtt tgcaatagtc ttattaaaat aaatgttttt taaaaaaaaa aaaaaaaaaa 840
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 896

<210> 225
 <211> 127
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (94)
 <223> n equals a,t,g, or c

<400> 225
 ggaggaacct ccagtctcag caccatgaat caaactgcc a ttctgaattt gctgccttat 60
 ctttctgact ctaagtggca ttcaaggtaa gggncatcaa agggctacttg aatttgtaag 120

137

atgagat

127

<210> 226
<211> 1949
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1466)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1540)
<223> n equals a,t,g, or c

<400> 226
ctgagaggca ggtagctgcg gcgcagggct gacggcgggcg agtccacgtg ctccccgcgg 60
ccggttgaaa ccgttggcgg gcgctggctg agaggcaatg tttgctgtct tccattggag 120
tgactgaatt tctacatgac ggctttttga caagacttaa aacctgtctt ggatagagaa 180
tatttagcca ttacctaata aatgggtattt ttacatgca atgcatgtgg tgaatcagtg 240
aagaaaatac aagtggaaaa gcatgtgtct gtttgagaa actgtgaatg cttttcttgc 300
attgactgcg gtaaagattt ctggggcgat gactataaaa accacgtgaa atgcataagt 360
gaagatcaga agtatggtgg caaaggctat gaaggtaaaa cccacaaagg cgacatcaaa 420
cagcaggcgt ggattcagaa aattagtga ttaataaaga gacccaatgt cagcccaaaa 480
gtgagagaac ttttagagca aattagtgtt tttgacaacg ttcccaggaa aaaggcaaaa 540
tttcagaatt ggatgaagaa cagtttataa gtacataatg aatccattct ggaccagggtg 600
tggaatatct tttctgaagc ttccaacagc gaaccagtca ataaggaaca ggatcaacgg 660
ccactccacc cagtggcaaa tccacatgca gaaatctcca ccaagggttc agcctccaaa 720
gtgaaagacg ccgtggaaca gcaaggggag gtgaagaaga ataaaagaga aagaaaggaa 780
gaacggcaga agaaaaggaa aagagaaaaa aaagaactga aagttagaaa accaccaggg 840
aaaactccaa gggattcaga agcctaagaa gcgcaaaaag ggacaggagg ctgaccttga 900
ggctggtggg gaggaagtcc ctgaggccaa tggctctgca ggggaagagg gcaagaagaa 960
gaagcagcgc aaggacagcg ccagtgaaga agaggcacgc gtgggcgcag ggaagaggaa 1020
gcggaggcac tcggaagtgt aaacagattc taagaagaaa aagatgaagc tcccagagca 1080
tcctgagggc ggagaaccag aagacgatga ggctcctgca aaaggtaaat tcaactggaa 1140
gggaactatt aaagcaattc tgaaacaggc ccagacaat gaaataacca tcaaaaagct 1200
aaggaaaaag gtttttagctc agtactacac agtgacagat gagcatcaca gatccgaaga 1260
ggaactcctg gtcattctta acaagaaaaa cagcaagaac cctaccttta agttattaaa 1320
ggacaaagtc aagcttgtga aatgaacatt tgtgtattta aaaattgaat ccattctgct 1380
gacttcttcc tttcactgct gtttataaaa tgtgtaatga attctaaca ctcaaatttt 1440
gctttttgaa gctgtatttt taagtnaaga aaatatattt ttggtataac ttttatgaga 1500
aaaataaaa atattctggt ccaaacttct aaaaaaaaaa ataaaaaaaaa aagggcgggc 1560
gctcgcgac tagackaggg atctttgtca cgtgggtttg ttttctgtct ccgtgcctcc 1620
ggcttcccaa agagatccag gtctttgctg ttccaggggc tggggacccc ggccccctat 1680
gccgccacgc cgccacaccg cctcaccctg gcttctgtgc tacttggcag ttccatttca 1740
ttatttattt tttgtgctgc tttttatcat gatataaatt attgaaaaca gatcacatgt 1800
gggcccgtgt ctggccgccc ccgccctgcc ccgtcctgcg gccaccacct aatttattgc 1860
cgtgcgtcct gctgctgtga ctgcttttgt acctttgcaa taaagaattt tctggtttca 1920
gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1949

138

<210> 227

<211> 1179

<212> DNA

<213> Homo sapiens

<400> 227

```
acccacgcgt ccgcccacgc gtccgcccac gcgtccgccc acgcgtccgg gtggcatgtc 60
ggtcaggcac agcagggtcc tgtgtccgcg ctgagccgcg ctctccctgc tccagcaagg 120
accatgaggg cgctggaggg gccaggcctg tcgtgctgtt gcctgggtgtt ggcgtgcct 180
gccctgctgc cgggtgccggc tgtacgcgga gtggcagaaa caccaccta cccctggcgg 240
gacgcagaga caggggagcg gctggtgtgc gccagtgcc cccagggcac ctttgtgcag 300
cggccgtgcc gccgagacag cccacgacg tgtggcccg gtccaccgcg ccaactacac 360
cagtcttgga actacctgga gcgtgccgc tactgcaacg tcctctgcgg ggagcgtgag 420
gaggaggcac gggcttgcca cgccacccac aaccgtgcct gccgtgccg caccggcttc 480
ttcgcgcacg ctggtttctg cttggagcac gcctcgtgtc cacctgggtc cggcgtgatt 540
gccccgggca cccccagcca gaacacgcag tgccagccgt gccccccagg cacccttctca 600
gccagcagct ccagctcaga gcagtgccag cccacccgca actgcacggc cctgggcctg 660
gccctcaatg tgccaggctc ttctcccat gacaccctgt gcaccagctg cactggcttc 720
cccctcagca ccagggtacc aggagctgag gagtgtgagc gtgccgtcat cgactttgtg 780
gctttccagg acatctccat caagaggctg cagcggctgc tgcaggccct cgaggccccg 840
gagggtctgg gtccgacacc aagggcgggc cgcgcggcct tgcagctgaa gctgcgtcgg 900
cggctcacgg agctcctggg ggcgcaggac ggggcgctgc tgggtgcggc gctgcaggcg 960
ctgcgcgtgg ccaggatgcc cgggctggag cggagcgtcc gtgagcgtt cctccctgtg 1020
cactgatcct ggccccctct tatttattct acatccttgg caccctactt gcaactgaaag 1080
aggctttttt ttaaatagaa gaaatgaggt ttcttaaagc ttatttttat aaagcttttt 1140
cataaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1179
```

<210> 228

<211> 1958

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (374)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (377)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1244)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1300)

139

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1311)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1327)

<223> n equals a,t,g, or c

<400> 228

```

aattccccggg tcgacccacg cgtccgcagc tccctctctc cctctggccc agtcccttcc 60
gcttgtgtcc gggaagctgt gggcggtgat ttaacatgac tcacttgggg gcataggcgc 120
tatgaagtgc agtggctggg tgccaggtgg cgccaatgac accctttttc tcagagcccg 180
ggctgaatgg acacctccct caaagccttc cagacccagg gttacggccg ttcccagaga 240
catgttcccc tgctgctggg cacacctgca gaggggaggg aaggtcctgt gtttgctggt 300
gctgctcgtc ctctcacttc ctaccgagca tcatgttgca aacaaatgac cttggcacca 360
ccgttttgca aatngtnctt tcttgggctt tacttttttg tctatgtgag caaaatgaac 420
tgaagtcaag gtacgactcc caataacctg ctgtgggatg agagggcttt gtcattatgc 480
atctgattag ttatccacgc ccagagctac actttctcga tgcttctcag ctctgactct 540
cacagggccca gggagaaaatt tttgtgcccc ctaaatcatg tagttggata caaacattc 600
cctggagggcc taccattctc aaatccccgt gcagggtctt gtgggggtgca acatgaaact 660
cgctctaact ccctacgtgg aggacagaca gacctatcct aactccaaag ccagacacaa 720
gggacaaaagg taccaaaaaag gtgcaagggt caagaatgga cgacgctggg cttccaattt 780
gctggaatat ctgtgctggc agaatggtgt cttgtcagca tatatcaagc atcttgcctt 840
tgctctgtcc tgcttgccca caaaggacac tcagacaaca ccggcctcat aaatgctgcc 900
tgagaaaaag cctagctagg tacggagggt cagggtattt cagaaaagag aaactgcttc 960
agccaatgct catgagattt accagggaat agcaacaag tctagtgcaa gccagggttg 1020
ggggagtgagg agggtgatta gcagagatca atctagaaag gaggtcaagg ttctgtagg 1080
ggggaaaagag ggtgcttgtg tattaaaact tgttttccag cagtttgagg atttctcaca 1140
gaactaaaaa tagaactacc attcatccca gcaatcccat tactaggtat atactcaaag 1200
gaaaacaaat tgttctatca aaaagacacc tgtactccta tgnatctgc agcactattc 1260
acaatagcaa agacatggag taaaccagg tgcccatcan cggatgaactg nataaagaaa 1320
atgtagncat atgcttacca tggaatacta cgcagctgta aagaggaaaag aaatcatgtc 1380
ctttgcaaca acatggatac agctggaggc cattatgcta agtgaattaa tgcagaaaca 1440
gaaaactaaa tatcacatgt tcttatttgt aagcagaagc taaatatttg gtgcacacag 1500
gcacaaaagat gggagcaata aacactgggg attccacaaa gggagcaggc agagggaagg 1560
gttgaaaaaac tacctatcag gtctctgtg cactacttgt gagacagaat cattagaagc 1620
ccaaacctca gcatcacaca atatacttat ataacaaacc tgcacattga cccctgaacc 1680
taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaagg gggggggggg 1740
ggggaagaag tgggggtggg cgacagtga atctagagta aaatcaagct ggcccaagg 1800
gtcctgcagg ctgtaatgca gtttaatcag agtgccattt ttttttttgt tcaaatgatt 1860
ttaattattg gaatgcacaa tttttttaat atgcaaataa aaagtttaaa aacttaaaaa 1920
aaaaaaaaaa aaaaaaaagg gcggccgctc tagaggat 1958

```

<210> 229

<211> 1751

<212> DNA

<213> Homo sapiens

140

<220>
 <221> misc feature
 <222> (1741)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1742)
 <223> n equals a,t,g, or c

<400> 229
 aattccccggg tcgacccacg cgtccgacaa cttttcttta gaaccacatt attggtcata 60
 atccttggtta ctgtcatgag gattgttgca tgggttaaac acaaacacag actagcaatg 120
 cacttgaaca aacctgggtg tctttggaaa taaatcacca ttagatttca cctggttatg 180
 ctgcatccca taagttccaa atgaatcacc tgcttatcct attaacgaag catttaattc 240
 acacacaaat gcttgaattt cccctgtata aatgtagtca tgcgattcaa cttttctaat 300
 aagatttgtg aatgctgcat catgatgaaa atgtggatta actgtgggtt gcatgcctgt 360
 tgttcatact tcagtgatgg tcacacacaa aacaagatga gttttactta ggtgaaacat 420
 tattaactg tactaacaat acagaaacat attctctttg tcgcttttta tcacaaaac 480
 tgaatggcaa atatgtcttg acattacttg gatgaactgt ggctagcaaa atggaattaa 540
 cttagccact ataatttttt aaaacattaa agtttctaaa ttgtttttgg gggccgagta 600
 acgcagagtc aataaagggtg gttatatgtt aagcttttag atggtgctta agaattctta 660
 tcttttttaa tagcagtatt ttttttttaa gaataaattg taaggagcaa ataaggcaga 720
 atgccactct accctcaggt caattttatg gtatatgaaa atgccagtaa tatttgtgcc 780
 acttgccaac tcggggggagg aggggctttt cccttactgg atacttttgt tatagtttga 840
 ctatgtcatt atgttgttta gagagcctcc acaatgagaa gttgccactg cagggctaac 900
 tcgccttcag aaataatcag aatgattcaa gggtaaaacc actttcatcc cttaaaatat 960
 agggactaat atttcttttt ctttttttta aaaaaaacat ttcttctgtg gcttagaaat 1020
 gtgccagtgt gttcaaaaca ttacaccaa ttccaccaga tttaggacct attaaaaatt 1080
 caaacaagtt tctttttttt ttttttttcc tgtgtaacag ggatttttta ataacggact 1140
 atatgcattc ttttgttatt tcacacttca gttaaagtga taacaatggg aaactgtgat 1200
 cattatcaga ctgactgaat gctttctgat ttccagttag tgatctagtt ctacgtatta 1260
 cacagggtgta atatctgtga gtgtaaataa ctggaactgt aactgatta acatgacagt 1320
 ttctcttttg ttgttcttat ctgtactgta ttatagtatg tgggtataaa tatctacaag 1380
 tatacacaca tatgtacttg tattccacta ttgtaacctg aaagaaagac tatgtattcc 1440
 cttttttaat tccgtactgg tatttgtgtt atttaaaaag caaaattctg ctctatttag 1500
 ttgtataata ttagaggata ctttgctgtg cacaattcca agtgccttag aacattgttt 1560
 agctttccta agtatatata aatgcatata tgtataaaat tgggaaaagt tacctcaata 1620
 aaatcatttg gaaatcccaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740
 nnaaaaaggg c 1751

<210> 230
 <211> 2153
 <212> DNA
 <213> Homo sapiens

<400> 230
 ccattctaag gaagagccct tctttccacc ccttttattt acttatttat ttctctctct 60
 ttatatcatt atgaactcag ggattcttaa tttatgtact ttttttgatg cttaaattgt 120

141

```

cccatatgtg gtctgtgagc cacccttaac actgggttcct ttgctctttg atatgcctac 180
atcatttttt tagtactttt ttgttttcta gcaaaagtgt tttgaagctt accatactgt 240
atttttttat tgtggtaaaa tatactttta cattcaagtt accttttta agcgtgtggg 300
tcagtaacat ccagtgcagt tgttcctcag tatccacggg ctggtgggtc caggactccc 360
acagatacta aaattcacac tcaagtcctt tattttatat aagtgtgaga tcttagataa 420
cctatgcata ctctcccata tactgtaaat aatctctaga tgatttgtaa tacctaacia 480
atgctgtgta aatagttgtt acactgtatt gttaacagta cagtaacaga cctgtctgtt 540
cagattcttc ctggcctttt aggggatcac tgacaaaaaa acttagtgca tgttcagtac 600
agacaacat cttttttttg ctttcgaata tttttgacct gagattgggt gaatccatgg 660
ctgtggaacc catggacaca gaaggccagt ggtacattta cagtgttaca gagctgtcac 720
ccctgtcgat tccagaattt ttccatcatt ccattagcag ctctctccca gcctgctctg 780
ctccggaccc cggcagccac tatctgttct ctgtctctgt ggatttgctt acattagata 840
gttcacagaa atggaatcac aatatgtgag cttttgtgtc tggcttcttt cacttagcgt 900
gctgttttca aagtccatcc gtgctgcacc atacatgagc gctttattcc atccatgctg 960
taccatacat gagegcttta ttccatccat gctgtgccat acatcagcgc tttattccat 1020
ccatgctgtg ccatacatca gcgctttatt ccattccatgc tgtaccatac atgagcgctt 1080
tattccatcc gtgctgcacc atacatcagt gctttattcc tttctgggt gaataacatc 1140
acattgtatc gataggtcac atctgggttt tccattcacc aaacattggg catttgggtt 1200
atttccacct tttggcgcgt gtgaataatg ctgctatgaa catgggtgta caagttttag 1260
tttgaacacc tggcgctact tattttgggg tataatacct ggagtggaa tgctgggtca 1320
tgcagtaact tgaagtttaa gttactgagg aattgcccga ctgtttccca cagtggctgc 1380
agcagctttt attccagtta gcaatcacga gagcttccca cttctcacc tacacctgtg 1440
atctgectct ttggttgtag ccattccctgt ccataatgagc tgggtctctca tcttgccgtg 1500
atltgcattt ccctgatgac tgttgatgtt gagcatcttt tcatgtctct attgaccatt 1560
tgcgtatctt ctttggagaa atgtctgttc acgtgctttg cctagttttt aaccgggctg 1620
tttatctttt gttattaagc tataagagct ctttatattc caaatgctag acccttaaca 1680
gatctgtgat ttgcaagtat tttctcccat tctgtgggtt atctttttac tttcttgata 1740
gtgtgcttct acaaaagttt ttaattatgg taaaatcaca tttattttct cttttgtaac 1800
ttttgggtgc atgtctgaga aaccattgcc aaatcaagat cacaaaaaat tgacgaggcc 1860
aggtgcagtg cctcacacct gtaatctcag aactttggga agccaaagat cacttgagcc 1920
caggagttag gaacagccta gacgacatgg taaagccccg tctctacaaa aaatagacag 1980
attagccgca tgcctgtggg tctgcctaca gaccagccca ctgaggaggt tgaggtggca 2040
ggattgcctg agtctgggag gttaaggctg cagtgaagct tgatggagcc gctgtactcc 2100
atcctgggca acagagttag atccgagacc gtgtctcaaa aaaaaaaaaa aaa 2153

```

<210> 231

<211> 1360

<212> DNA

<213> Homo sapiens

<400> 231

```

ccacgcgtcc ggaggggagc agcctgcgca gggcaggagc agctggccca ctggcggccc 60
gcaacactcc gtctcaccct ctgggcccac tgcattctaga ggagggcgt ctgtgaggcc 120
actaccctc cagcaactgg gaggtgggac tgtcagaagc tggcccaggg tgggtggctag 180
ctgggtcagg gacctacggc acctgctgga ccacctcgc ttctccatcg aagcagggaa 240
gtgggagcct cgagccctcg ggtggaagct gaccccaagc cacccttcac ctggacagga 300
tgagagtgtc aggtgtgctt cgcctcctgg cctcatctt tgccatagtc acgacatgga 360
tgtttattcg aagctacatg agcttcagca tgaaaacct ccgtctgcca cgctggctgg 420
cctcgccccc caaggagatc cagggttaaaa agtacaagtg tggcctcacc aagccctgcc 480
cagccaacta ctttgcgttt aaaatctgca gtggggccgc aacgtcgtgg gccctactat 540
gtgctttgaa gaccgcatga tcatgagtc tgtgaaaaac aatgtgggca gaggcctaaa 600

```

142

```

catcgccctgg tgaatggaac cacgggagct gtgctgggac agaaggcatt tgacatgtac 660
tctggagatg ttatgcacct agtgaaattc cttaaagaaa ttccggggggg tgcactggtg 720
ctggtggctc ctacgacgat ccagggacca aaatgaacga tgaaagcagg aaactctttc 780
tgacttgggg agttcctacg caaaacaact gggttccgg gacagctggg tcttcatagg 840
agccaaagac ctcaggggta aaagccctt tgagcagttc ttaaagaaca gcccagacac 900
aaacaaatac gagggatggc cagagctgct ggagatggag ggctgcatgc ccccgagcc 960
attttagggg ggctgtggct cttcctcagc caggggcctg aaaaagctcc tgcctgactt 1020
aggagtcaga gcccggcagg ggctgaggag gaggagcagg gggtgctgcg tggaggtgc 1080
tgcaggtcct tgccccttgt gtcgcccctt tcctcctcgg aaacaaaacc ctcccacagc 1140
mcatctaccc ggaagccac cctcaaaggg tccttttggg accacctgtt tgtggaaaaa 1200
atggggtcct tttgtcaggg acttctgacg gctggtcctg aggaaggcca aactgcccag 1260
attgagccca attaaatatt atttttctgg ttttgaatac caaaaaaaaa aaaaaaaaaa 1320
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1360

```

<210> 232

<211> 1986

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<400> 232

```

ggcacnagcg ccgcccgggc gcagcatggg gcgcttccgc gggggcctgc ggtgcatcaa 60
gtacctgctg cttggcttca acctgctctt ctggctggct ggatcgccg tcattgcttt 120
tggactatgg ttccggttcg gaggtgccat aaaggagtta tcatcagagg acaagtcccc 180
agagtatttc tatgtggggc tgtatgttct ggttggagcc gggggcctga tgatggccgt 240
ggggttcttc ggatgctgcg gagccatgcg ggagtcgcaa tgtgtgcttg gatcattttt 300
tacctgcctc ctgggtgatat ttgctgctga agtaaccact ggagtatttg cttttatagg 360
caagggggta gctatccgac atgttcagac catgtatgaa gaggtttaca atgattacct 420
taaaagacagg ggaaaaggca atgggacact catcaccttc cactcaacat ttcagtgtctg 480
tggaaaagaa agctccgaac aggtccaacc tacatgccc aaggagcttc taggacacaa 540
gaattgcata gatgaaattg agaccataat cagtgttaag ctccagctca ttggaattgt 600
cggatattga attgcaggtc tgacgatctt tggcatgata ttcagcatgg tcctctgctg 660
tgcgatacga aactcacgag atgtgatatg aagctacttc tacatgaaaa ttgcaatcta 720
aagctttcat accaaatgtc acaggagctg tctcccagct catttttaac actgaaatga 780
cattaggatc taaaataatt tgctgtcaat tgtacatttg catgagtacg tatgtttggc 840
tcattactgg ttaccctctt gagtgaatgc ctgtttatga tgactgagag catattcatg 900
tgtgatctgc gtgtttcttg aatatgcttt ataccgtaat gaaatctgtt tgctgggaat 960
tcctgattct tggatatata gaagaacaac ctatttcgct cccagaaaaa aaagatcaaa 1020
gagctttcag aaactttgag aacttggcta tttagaaaaa gtgataatgg gtcaagtttc 1080
tcagactgta gccattgaaa attagatgca gagaattcag agatttcttc ttaatggaag 1140
taataagctg taagaattga gagatcacia tggagtgtta aaactgactg tgtctaagtt 1200
gggtgtaagg gtttcctggg tttttttata tacatgctct cccagaata cagtaaacca 1260
cagttttaga actaaacaca tctgtaaaac taaatatagc atggaaaatc caatttgaat 1320
aagtcatgct ttcctagaat ttaaaaaata aaaagtcttc ctctggaaaag agaagtcaca 1380
cagacaatca tgtgccctat aaaagtgagt gtttatagga ctaaaaaact tttaacaact 1440
ttttaaggaa atatttttgt tcttatacaa aaacatgtaa atattgcttt attactttca 1500
ttttctgacc ctgctgtaaa ctactgcaac cctcacatcc tcaaagggac ttttatgtca 1560

```

143

```

aactcttctg tttctccaaa tataaggaaa aaagactaaa gcaagagatc tggcagttga 1620
aaattgtggg aaagagaatt tgtatgggca ctgtatctat gaaatacctc ataacttacg 1680
tttacctgtt ttcctaactt tttgtatatt tcttggatag ccacctagag aattcttcat 1740
agattaagaa ctacagtttt caccacttaa cataagtaaa acaaagtcct tcataattta 1800
accattagca tctttggcca aacccaaata aagaaaagca tcttctccta gttgtgtgtg 1860
ggcaacagaa acaagttaag gaaacaaaaa tacttatata tacacaggac caaataatg 1920
ttctttttat gcaaattccc tgtggaaata aaattttcaa tgtttaaaaa aaaaaaaaaa 1980
aaaaaa                                     1986

```

```

<210> 233
<211> 705
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (108)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (680)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (696)
<223> n equals a,t,g, or c

```

```

<400> 233
ggattacatg tagttattga gaatcctttc gtaattcagt ggcttaatca tgtaatgtct 60
aaatattgtt gtacattagg atgtatacat gtaaattaaa gttacatntg tttagcatag 120
acaagcttaa cattgtagat gtttctcttc aaaaatcatc ttaaacattt gcatttggaa 180
ttgtgttaaa tagaatgtgt gaacactgta ttagtaaact tcatcacctt tctacttctt 240
tatagtttga acttttcagt ttttgtagtt cccaaacagt tgetcaattt agagcaaatt 300
aatttaacac ctgccaaaaa aaggctgctg ttggcttatc agttgtcttt aaattcaaat 360
gctcatgtga cttttatcac atcaaaaaat atttcattaa tgattcacct ttagctctga 420
aaattaccgc gtttagtaat tatagtgggc ttataaaaac atgcaactct ttttgatagt 480
tatttgagaa ttttggtgaa aaatatttag ctgagggcag tatagaactt ataaaccaat 540
atattgatat ttttaaaaca tttttacata taagtaaact gccatctttg agcataacta 600
catttaaaaa taaagctgca tattttttaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660
aaaaaaaaar gggggggggg cccccaaaaa aaccntttt ttttt                                     705

```

```

<210> 234
<211> 838
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (32)

```

144

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (822)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (832)

<223> n equals a,t,g, or c

<400> 234

```

taaaccgcgaa gtgccaaata ataatttaaa anatgttaat ttttttggcc ncctaaattt 60
gccctttcca tccattaaaa atgtccaagt tccaagtgat atgtgccctt aatatccacc 120
ttggatgttg gtgggttttt gaatttttgg gtgggttaatc cagttttatt ttgaaaagac 180
gtacttgaat agttacagca tatgtttgaa caggaagtag gaacatgcat acacgaagaa 240
atgctaacgg aaggatttgt tatgtttagg atcttccctt ggaaactaaa aatagaatat 300
taatgacatt actgtttgta gaatgacata tgcagatttt ctcataagca gtcatttgtgt 360
ttgccagtaa tgtttgagag acatgtaagt tgaaagtttt gctaaattat aaagctcctt 420
taattcggtt gttttgatct tcttattctc ttgtcttttc taaatgttaa caaaatatat 480
cttaacagat tacatgaaat ttaggaatta tttaaaagtt accattagct ctaaaattaa 540
gattcggatg ctttatttat agtaactgaa gctaataatg ttttatgttt tgattttttg 600
aaatttaatt gtagaagtca ctgccttctg agttttcaaa tagataacca cctttaatat 660
tacactgctt ataatactaa tgtttacaga tatgtttctg tttataacca tataatacat 720
tggctttgtc atattagttt tttttgcaag tagttatgta aaagagatag ataataaaat 780
attaaataac aaaaaaaaaa raaaargctc gagtaarggc anagtggcat gngccata 838

```

<210> 235

<211> 1410

<212> DNA

<213> Homo sapiens

<400> 235

```

ccacgcgtcc ggtccctagg agataagagt atcttgca ca gcaggtgcag gtttcccagc 60
agctcaggca agagtccgat gtttgtgcc a tctgacctg atgtctggag agatagccat 120
gtgtgagcct gaatttggca atgacaaggc cagggagccg agcgtgggtg gcaggtggcg 180
agtgtcctgg tacgaacggg ttgtgcagcc atgtctgggc gaactgctgg gctctgctct 240
cttcatcttc atcgggtgcc tgtcgggtcat tgagaatggg acgggacactg ggctgctgca 300
gccggccctg gccacggggc tggctttggg gctcgtgatt gccacgctgg ggaatatcag 360
tgggtggacac ttcaaccctg cgggtgtccct ggcagccatg ctgatcggag gcctcaacct 420
ggtgatgctc ctcccgtact ggggtctcaca gctgctcggg gggatgctcg gggctgcctt 480
ggccaaggcg gtgagtcctg aggagagggt ctggaatgca tctggggcgg cctttgtgac 540
agtccaggag caggggcagg tggcaggggc gttggtggca gagatcatcc tgacgacgct 600
gctggccctg gctgtatgca tgggtgccat caatgagaag acaaagggcc ctctggcccc 660
gttctccatc ggctttgccg tcaccgtgga tatcctgggt gggggccctg tgtctggagg 720

```

145

```

ctgcatgaat cccgcccgtg cttttggacc tgcggtggtg gccaacact ggaacttcca 780
ctggatctac tggctgggcc cactcctggc tggcctgctt gttggactgc tcattaggtg 840
cttcattgga gatgggaaga cccgcctcat cctgaaggct cagtgaagca gagctcgtgg 900
gattcctgct gctccaggtg tcctcagctc acctgtccca gactgaggac aggggagttc 960
ctgcatttcc tgccagggca gaggcccaga ggagcgaccc cctgcttcca ctgcttgggc 1020
ctgctttctc agatagactg actgctgagg aggtctctagg ttcttggaat tcctttgtgc 1080
tcacagaga cccagcctg gggaacacgc tgcccgact gccagagag cagtgcaaac 1140
accacaacac gagcgtgttt cttgagagga atgtccccga gttggacaag gaggctgttt 1200
ctgcacatca gctcatttcc cgcaccccat ttcttgcttg attgctttgt tgggggcctg 1260
gccatttct tgccttctca gctgacaatt ctactttgc aataaatagt ccagtgtttc 1320
cttccaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa                                     1410

```

```

<210> 236
<211> 422
<212> DNA
<213> Homo sapiens

```

```

<400> 236
aaactatttta gtctgtaaca gagccatatg ctgcagggct aactcacagt agaaatgggc 60
aatttcgacg cgctgtttat ctttaccag ctaccagcg cgctcgcaa catcaattgc 120
tttctgccac tcaactgtag cctggttagt ttgtagcaac tgttgacg cgccaatgcg 180
gaagtcagtt tcactgggtca gctgattgaa catgtcttcc gcgcggtcat ataaccggc 240
ggccatgtaa tcacgcccc gttgttgaa cgccaacaga cgctgttcat aggtcagcga 300
ggcgctttcc attaggtgtc gatggatgcg aatagcgcg ttcaacttcg ccacggaacg 360
ggaacagggt ttccgagcgt aaggtgggct tcaacggtgc ccgttattcc tgttttaagc 420
at                                     422

```

```

<210> 237
<211> 351
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (322)
<223> n equals a,t,g, or c

```

```

<400> 237
ctgtccctgc actcctggc ggaaggcggc tagagcggct ccctctgagc tctccgagag 60
attggctcggg acctgaagcg ttgaggttaa gggcaaggca aggagcaacg aggagttttt 120
cgttacgtta gaaaaatttc gttgcgtgct gaaagcgctt ttacctgtgt tgtatgattt 180
aaccttatga aaatggacag tatttccagt ttacaagtg aggaaagaag attaagaaac 240
ttgcctccgc cangcgtggt ggttccactc ctgtaatccc agcactttcg gcggccgaag 300
caagcggatc acttgaggtc angagttcga agaccagcct gggccaaaca t 351

```

146

<210> 238
 <211> 2682
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (647)
 <223> n equals a,t,g, or c

<400> 238
 gaatacccca ggatttatgt ataaaaacct gcagtgtctg gttattgatg aagctgacg 60
 tatctttgat gtgggggttg aagaggaatt aaagcaaatt attaaacttt tgccaacacg 120
 tagacagact atgctctttt ctgccacca aactcgaaaa gttgaagacc tggcaaggat 180
 ttctctgaaa aaggagccat tgtatgttgg cgttgatgat gataaagcga atgcaacagt 240
 ggatggtctt gaacagaaga accgaaagaa gaagcttatg gtcttctttt catcttgtat 300
 gtctgtgaaa taccactatg agttgctgaa ctacattgat ttgcccgtct tggccattca 360
 tggaaagcaa aagcaaaata agcgtacaac cacattcttc cagttctgca atgcagattc 420
 gggaaacacta ttgtgtacgg atgtggcagc gagaggacta gacattcctg aagtcgactg 480
 gattgttcag tatgaccctc cggatgaccc taaggaatat attcctcgtg tgggtagaac 540
 agccagaggc ytaaatggga gagggcatgc cttgctcatt ttgcgcccag aagaattggg 600
 ttttcttcgt tacttgaaac aatccaaggt tccattaagt gaatttngac ttttcttgg 660
 ctaaaatttc tgacattcag tctcagcttg agaaattgat tgaaaagaat tactttcttc 720
 ataagtcagc ccaggaagca tataagtcac acatacgagc ctatgattcc cattctctga 780
 aacagatctt taatgttaat aacctaaatt tgcctcaggt tgctctgtca tttgggtttca 840
 aggtgcctcc cttcgttgat ctgaacgtca acagtaatga aggcaagcag aaaaagcgag 900
 gaggtggtgg tggatttggc taccagaaaa ccaagaaagt tgagaaatcc aaaatcttta 960
 aacacattag caagaaatca tctgacagca ggcagttctc tcaactgaaca catgccttcc 1020
 tttcatcttg aataactttg tcctaaaatg aatttttttt ccccttgatt taacaggatt 1080
 tttgtagact ttagaatttg gacttaccta acaagagtat aaattgactt ggggttgcaag 1140
 cactgagcac tgttacttct atcacgtctc tcttttatatt ctgggatata aaacaggcctt 1200
 taagtttctt ggttgcccaa gggcagagca aggaatatct ggtgtttctt gtgatgataa 1260
 tattttaatt ttaaatatcc ctccctcata caagtgtatg ttaccatttt aatataattc 1320
 tttttgtacc tttccttctt gttttgtgaa gatttttgtg gcatggattg ctgtgctcac 1380
 tgctgtaaaa ggtgacctag tgtactgggc agctggtggc ggtgcagaaa agagtctcag 1440
 gttatatttt gtttttagtt atttcttggg ccttgacagt atctaatacgc tcctcctgaa 1500
 aatgctgcag tataaaagag caaagagctt tgggaaatac ctaagaagca ccttaagatt 1560
 aggtggtgat tgcctttata gattcttgat tttaaagcaa caggcctttc tcagggtgtt 1620
 cattttttgg agcaaaaact atgggttgta atttgaataa agtggtacta agcagttata 1680
 acgtttgatg gctggggggg aggaagagga tggatttgag atgtttgagc ctcatattaca 1740
 tcaatagagg tgtaattgtac tgcatttctt catttggtta cataacaaag actttcatac 1800
 aaagaacgat gatgctcctc attaagattt gtttaattca aggtggtttg gatttggtta 1860
 gcctttgcac tctgtagagt acttagaaga caagggcaac ttacttggag ttagagccaa 1920
 gctgtcagac ggtgcccagc acacattaat gttagcttct ttctgagaaa aaaatacctc 1980
 ttccaggccc tgaaacaaaa aatacatttg ctgtgaagat tgaaaatgaa caaagttaga 2040
 aaaaaaaaca gcaaaatcag tgatttagtc agatgagttt ttcgtttagg gagcacttga 2100
 tttctagtgt gttttgtaca gtatataact acaagatagt acattttgta gcagttcaaa 2160
 gccaaagttg ctagcatcat tttgctgttg tgccagttaa tcataggatc ccattaaata 2220
 agtgtgctaa catcgaaat agagaaaact ggtaaagaac attccagtag gaaaagaaaa 2280
 gaacaatctt ccatttctgg gcttggccac catcacctcg gtcggacctg tcctggactt 2340
 ccaaccttga ctgctgagct cctggcttag cttcttgggt tcctaattcc tgggtgttta 2400

147

```

taattctctc caccgatcatg tttttctgat ttttttttcc agaaataatg ttttttaaaa 2460
gacaaaaaca aagggaagaa tatttaatta ctgagcagaa gtaaatactg ttgggtatttt 2520
gtacataatc taattttttat atgcatgtty atgcttttta atttttttat caaaaattaa 2580
gtcatctacc tactacttgt aaccagcttg tttcataaca tgttattttc ctgtgtcatt 2640
aaataattac ttcaatgttg aaaaaaaaaa aaaaaaaaaa aa 2682

```

<210> 239

<211> 2254

<212> DNA

<213> Homo sapiens

<400> 239

```

gataatatTT aatgttgTtc tgcacatctc tatacagtta actttttggc tttcattctg 60
tatagataag aaaatgttat attataaaca gcctactcag tgcaaataatt tatctgttta 120
tcaaattccac aatatgctgt ataataccgg ttttactata taatctattt tagacatagc 180
tgttttagaac tagagtgtgc tttttttgtg tttttctgat gtgtgggtgct agacaagtta 240
cttttgtgaa caacaaaaat tatccctttt attcctagac aataccacct ttgggtcttg 300
ttaatttcac tgagtataac tatatatattg tatatatata catatatata tataatctacc 360
tatgcccaac tggcagctgt atcagagtgc tggatttggg acatgctttt ctctttaaat 420
acataatatc attatataaa ttattctaga gtgtatttaa ttaggataaa attacttcct 480
tagtatggat atttgacatc tatagggtga atttgtttat aaatatggct atatggaaac 540
ttatttagcat ttactttatg tttgctactt ggctttacag catatctcct aagctgaaaa 600
ataatttgcc aggccttcaa gatcctaaag aaacttgttt aatggagtaa tatacttttt 660
tttcttatta aggaattgta ttactggcac ctaacacagt tgtattctta gctcctatta 720
tagataatgg gcatttacat aaaatatcct agatggcttg atggcagaat aaacctttcc 780
cctcctacct gagtcatgag aaggatggag acgtcctctg ccataacatg ggccataaag 840
caaatctgac atgggatgtt ctgtttcagt atgacctcaa ccagtcccat gaactgagtg 900
aaggaccttc attttcaaaG ttatttaata agtagcttaa ttaagccttt ctacccattc 960
tcccaagatc tattggcatt attgaaaagc aaagtttatc aaatatctaa ctaaggatgt 1020
agttaacctt attaaatatt gattagaatt gttctgtaat attactgaat ttgtaagatc 1080
tttagcaaaG atttttgagc aatttataaa tgtagagcaa atgtttctgt ttactgcact 1140
ttttgtaaCT gaaggtgata aattctcaag ccatgattat tggcttccat gcaactgcaat 1200
atztatccac aattctagac attttccatt tttgtggaag agttgctgtt accttaatta 1260
taaatgcaat tgttgtgtta atgagagcta atgctagtag ttaacctttt aaagtggatt 1320
ggctacagtt gagggagaaa tctcttttaa tataaatcac atcattcctt aactgcctct 1380
cttggaagaG gattgaaacc ttttttttaa agcacgattt agcatcctaa gcttcctgag 1440
ggtagagatt gtatcttttt gcgtctgcac aatggctagc acatgtcagc atttgacaat 1500
tgttaaatga taacaagtgt gcccgaatta aaacgttttt cctgggttgt tttgttaaat 1560
ttacaaaagta agccaagcct tacgggttaac attctcctct acaaccaagt attaaagcca 1620
catttaaaaa gaccacatga aatgctgatt ctaatttgtg ttaggtcttg aggattaagc 1680
acacaaatTT cacaaacttc tgtttgagta aacaaactca gccttctgta aatatacatg 1740
caagttttgga aacagtaata ctgtacctat aaatatatgc tgtctgtttt gtgtacagta 1800
tgtaaaaact ctttttctgc cacactaaaa atgcaagcca tttatgggaa tcctaaaaact 1860
agtattgaac taaaactttg ctaatgatct ttattagagg atcgccaac ttttcaactta 1920
ccytgggttt tcttttcaat tcactcttac actagtctgc ttatttccag ctgtttattt 1980
tattgagtcc tgaatttaaa aaaaaaatat tttgattcat tttgtaaaata caagctgtac 2040
aaaaagagaG gatttaatgt tgtcttttaa atactccaat tttcattcta atatgaatgt 2100
tgttatattg tacttagaaa ctgtaccttt aatattacat taccttttatt aaaagtgcac 2160
tgaacacatc aatttttagat gtgcttttat tactgttatc ctataataaa acttcagctt 2220
ctaattggaaa aaaaaaaaaa aaaaaaaact cgag 2254

```

148

<210> 240
<211> 1057
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (958)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (966)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1035)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1053)
<223> n equals a,t,g, or c

<400> 240
ttaaactcaaa ctctaaagtc ttgagtgttt caaagtcagt cgttacctgt ttaaaagcct 60
cagccttttag cttattcctc cttcaataca cgggaccttt gggttaatttg gggcaggaaa 120
actcttaaaag taatctctct tgggcagagg ccttattgca ccagagggaa aaagtatata 180
cttcatittgc tgttactcca gttatgcctt aaattcattt gcttggtaat cctatcaacg 240
rgcactaact tcttagtata ctttaaacac ttagttgggt aacactgaga ttttgttgtc 300
ctttattttt tgctgagatg gagtcagtca gatgttagtc atagctaaca ccgaatttgt 360
gttgtcatitt agacagttac tgattcgatc tgctttatat atgagaacgt atttttaact 420
attccaagaa ggaagaggta gctaaatgta atccccctct cctatcccc cagaaaactg 480
aactgtaagt tctaggtaga ctaattggga gcagacacgg agtttttagat gccttagcca 540
aaccacagcag aaacctttca cacagccact catcgtaaga aacgcagatt tttctcttct 600
catgcttgtc tctgggtccc tgcatttgta gtgacagaac tttcactagc aggatataaa 660
gaaagtaatt atgcttggag tccctcttta ctgggtttga gttaggtgca taacatggaa 720
aggagtgggt ccttcaaagt aatgtgacca ctccgtattg tggagtgact tccctagggc 780
atcctatata tcctaccaca gaaggccaag ggacagagca ccaacttcag tatccaagaa 840
attagatcca caactcttga ttttccacac tgaggactgt cgcgagtaag ttgtaagttt 900
gccgtcttcc ttctggctta gcaggtgctg cagctgtact ctcgactcct gtctgtgnag 960
cgtganyagg gaaaatgagg agtggagtcct atttccaaaa aaaaatgtgg atggagtttt 1020
ttccttaaaag tggcnttcat tggcccaatt ccntttt 1057

<210> 241
<211> 498
<212> DNA
<213> Homo sapiens

<220>

149

<221> misc feature
 <222> (493)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (496)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (497)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (498)
 <223> n equals a,t,g, or c

<400> 241
 gagttgatcc tgagatgaag gtggagcggt acaagcgcac ctttgaccaa aatgaggagc 60
 tagggctcaa tgacatgaag acagaggggt atgaggcagg cctggctccg caacggtagc 120
 agtgggtggc tcaagggcca gcctccagcg ctgctctttc tgtaggttat ttattagtat 180
 tggatgaagg cgaaggctgg gagtgtcttt cccaccagcc cttgcccattg gtggggagga 240
 catctgggtct gagtcagaga tctgtgcaca ctttctaaac agcttgtgat gcaagtgtga 300
 gcctattgtg ttacttgacc ttattttggga agttttgaat tggcctagga ggaaaccag 360
 aaatgaacca ggggtatgtc atcacttttt tcatatcaag tcctcaccct ccttcacat 420
 aatgctctat cctctaargt tggaactctg aarttggaga argtggaata aagttacacc 480
 tggaaaaaaa aanaannn 498

<210> 242
 <211> 1784
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (1739)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1777)
 <223> n equals a,t,g, or c

<400> 242
 ggcacgagcc aaccagcta tggcctatgc caacgaggtg aaacgtgtgg tcagcagtg 60
 acaggagaag ggcaggaaga ttgcagcctt cttcgctgag tctctgcca gtgtgggagg 120
 gcagatcatt ccccttgctg gctacttctc ccaagtggca gagcacatcc gcaaggccgg 180
 aggggtcttt gttgcmgatg agatccaggt tggctttggc cgggtaggca agcacttctg 240
 ggccttccag ctccagggaa aagacttctg ccctgacatc gtcaccatgg gcaagtccat 300

150

tggcaacggc caccctgttg cctgcgtggc cgcaaccag cctgtggcga gggcatttga 360
agccaccggg ttgagtactt caacacgttt gggggcagcc cagtgtcctg cgctgtgggg 420
ctggccgtcc tgaatgtctt ggagaaggag cagcyccagg atcatgccac cagtgtaggc 480
agcttcctga tgcagctcct cgggcagcaa aaaatcaaac atcccatcgt cggggatgtc 540
aggggtgttg ggctcttcat tgggtgtggat ctgatcaaag atgaggccac aaggacacca 600
gcaactgaag aggctgycta cttggtatca aggctgaagg agaactacgt tttgctgagc 660
actgatggcc ctgggaggaa matcctgaag tttaagcccc caatgtgctt cagcctggac 720
aatgcacggc aggtggtggc aaagctggat gccattctga ctgacatgga agagaaggtg 780
agaagtgttg aaacgctgag gctccagccc taagccagcc ctgctctgcc taagtgtact 840
ccagaagaaa ctcatctcat ccaaatacac gctattgaga aggcgagcct gacctccctc 900
ttacagataa agtcagcttt cagaggtcga ggggtggggg gcctgcccga ggccataatg 960
ctaccacccc cctcctccta accactggtc tgttgggaata acccagatgt ctgcatcccc 1020
tcaagtcagt caatttcctt tctgtccact gggggtggaa tggggtaggg tgggatactt 1080
taaagtgtct ctgcttaaat aaattagacc agaccagtgt atttctaaag aaaatcctga 1140
catgcacacc cattaaaaat agtacatttt acagtgtccc agtcatactt ttaattggca 1200
aattaaaata atgcaatctg atatatctta tctactaaa ttaaaaatac tgaatataac 1260
caactaaata tacttactcc taagactcac taccagtagt ttcacttaaa ctctgcctta 1320
gaggctcttc ccacccatth cccattatgg cacatagaga aaaaggcctc tatcactgtc 1380
cactggagta ataaccactg ctccccctaa ctgcctcaaa gactgtcatt ttatagaaaa 1440
tttaagacta tctaatcca ctctttccaa actcccagcc aggatagaga cttccaggag 1500
ttccacctgt cccaccttat ctggctgcca actcctgctc agaaacagaa cctgccacac 1560
cctgccactg caggcccgcam cctcaactcc caactgccaa cttgaagcct gaactaccct 1620
ttccctgacc agagttcagg aggggaagag ctacacctcc ctgcacatga atccactcat 1680
ttgaaagcac aactgaccct ggatttaagc tggccaggac cctgggagat ctttgggaang 1740
atthttgcct ggggtttaagg ttaacttaaa gaggtgncca gaag 1784

<210> 243

<211> 936

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (840)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (854)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (865)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (905)

<223> n equals a,t,g, or c

151

<400> 243

```
catatgtttg cttgggatag aggtcaaaga ggatcctctg gcatgttttg ctgggttcct 60
gtagtcattt caacaggatt aactataatc tataattgat agattattga gtgacacaca 120
gcgtgatgct gggcaggccc caagctgaaa agcatctcct ccaacttact ttattcttag 180
caattcattc ctttggtttg aaaattcttc agcatcttca agagtccttt actaatgsat 240
cctttggggg agtttgtgcta aattatcaac tcacaaggat gagatkgctg gctctagggg 300
gccagcctgc caacatggat gggctgtccc aggstctcaa gtgagctcag gtctgtacac 360
tgcactccrg ggagagtaaa tgtgcctggg gcatagaatg gagacttttg agtttggagt 420
ttggagtggg tttggggaca tcagcttctc tcttccagtt agtctgataa gtcctttgtt 480
gcctggccct ggaaaccact tgtscctcga aaatgccatt ctctggaatg tagctgtgga 540
gtagggagag agttggcccc tgtgttctgt aaccaagca agtactgtct cactgccatc 600
ttggggcaga ctccgcagta aggagaatct ctcttgccct tttgtgtttc ttggtttctt 660
cctttgtaaa tacaaggcat agtctctgcc cttccccag attgccagaa gagtgggata 720
tattgttcta gcaatataaa gctctgaggg ctttctgcag gactgtagac accactttgc 780
tgtgatagtg aagaatgtgg gggagtgttg tgagggctag gcgaagcggc ccggccttgn 840
ccattgaca gctncagtct tcctnccctc ataacttttt taacctaaca gaggatttaa 900
aaaanaaaaa caatttttagc tggggcacaa tggtctc 936
```

<210> 244

<211> 1381

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1348)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1349)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1350)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<400> 244

```
tccgtggtgt ggttgactct gaggatctgc ccctgaacat ctcccagaaa atgctccagc 60
agagcaaaat cttgaaagtc attcgcaaaa acattgttaa gaagtgcctt gagctcttct 120
```

152

```

ctgagctggc agaagacaag gagaattaca agaaattcta tgaggcattc tctaaaaatc 180
tcaagcttgg aatccacgaa gactccacta accgccgccg cctgtctgag ctgctgcgct 240
atcatacctc ccagtctgga gatgagatga catctctgtc agagtatggt tctcgcatga 300
aggagacaca gaagtccatc tattacatca ctggtgagag caaagagcag gtggccaact 360
cagcttttgt ggagcgagtg cggaaacggg gcttcgaggt ggtatatatg accgagccca 420
ttgacgagta ctgtgtgcag cagctcaagg aatttgatgg gaagagcctg gtctcagtta 480
ccaaggaggg tctggagctg cctgaggatg aggaggagaa gaagaagatg gaagagagca 540
aggcaaaagt tgagaacctc tgcaagctca tgaaagaaat cttagataag aaggttgaga 600
aggtgacaat ctccaataga cttgtgtctt caccttgctg cattgtgacc agcacctacg 660
gctggacagc caatatggag cggatcatga aagcccaggc acttcggggc aactccacca 720
tgggctatat gatggccaaa aagcacctgg agatcaaccc tgaccacccc attgtggaga 780
cgctgcggca gaaggctgag gccgacaaga atgataaggc agttaaggac ctggtggtgc 840
tgctgtttga aaccgccctg ctatcttctg gcttttccct tgaggatccc cagacccact 900
ccaaccgcat ctatcgcatg atcaagctag gtctaggatg tgatgaagat gaagtggcag 960
cagaggaacc caatgctgca gttcctgatg agatcccccc tctcgagggc gatgaggatg 1020
cgtctcgcat ggaagaagtc gattaggtta ggagttcata gttggaaaac ttgtgccctt 1080
gtatagtgtc cccatgggct cccactgcag cctcgagtgc cctgtccca cctggctccc 1140
cctgctggtg tctagtgttt ttttccctct cctgtccttg tgttgaaggc agtaaaactaa 1200
gggtgtcaag ccccatcccc tctctactct tgacagcagg attggatggt gtgtattgtg 1260
gtttatttta ttttcttcat tttgttctga aattaaagta tgcaaaataa agaatatgcc 1320
gtttttatac aaaaaaaaaa aaaaaaannn ggggggggng ccccggtccc matttcccc 1380
c

```

<210> 245

<211> 779

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (41)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (650)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (669)

153

<223> n equals a,t,g, or c

<400> 245

```

cttttccttn caggtggaaa ggaccccttg gtacccatnc ncaagcagtt aggaaaggac 60
ctggctcttt acatatattg gatggctctc atggcaaac ttctcaattc ctttaattagt 120
catgtctcag cttcaaggat atcagacagg aatgaaacac acttgaaaat gagattgacc 180
tggagatttt ttttccttaa tctctcatac ctttaattgga aaaataatca attaatctta 240
tgtaatttag grtatacaaa gttcacctc cttgmaagtg actagggcaa gccctgaaga 300
tcttctcac ctccctttat ctttctataa ccttgctctc tccagcacca cagggaagac 360
aatcacagtg ggtcaagagc gaccctcttt cactggggt ctgcatgacc tctgagacct 420
gcttatgatc agtgcaatga agttagaagt aactgatgat tgggagcctt tgcagatagc 480
tgggcaaatg ggtgatttac ttatcccat tctaaatgga gtgagctctc tttgaggcta 540
agcaaggagg cgttgatgac tagtttctag actttgcctg gagaccctt tggaaatctg 600
tcttcttttt aaactcactt aatatgcctt aatcatctgk gtgtaatggn agtcatccgc 660
tcctcaatnt aaccctyctm ccctggggct ttggctgtcc tcaatgagag tttcatgcag 720
aatggaaaat cctctatatg tacaatctct ctccctctca tttctcttcc tcctcacct 779

```

<210> 246

<211> 1231

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (795)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1219)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1229)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1230)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1231)

<223> n equals a,t,g, or c

<400> 246

```

ccacgcgtcc ggaagaaggc ctaattccta acctgggacc cagagagaga cataagatat 60
ccagagagat atgcaccaag aaactgcaat ttatacaaa acagtcagaa agcagctgaa 120
gacagaatga gagagaaaact aagtaaaaga aacttgatgc ctccaaaatg aagagtatgc 180

```

154

```

ctcatttcca tatgtgaact gaaaagctct ccacttttga aataaaggct tactatagag 240
cagccctggg aatagaacta caagacttat aataacttcc tgtttgagtt gaaatgaaaa 300
ctcataaaga atctatgcta ttaacccccct aatttatact tttgtattct tttatgttgt 360
attttgtatt ttatgttgga cttctttttt aaaattttgt atttattttt aattgaaaaa 420
taattgtgta tactttattgt tgtacaacat gatgttttga tatatgtata tgttgtagaa 480
tgactaaatc aagctagtta acatatgcat tacctcctat acttatcatt tatttgttgt 540
gagaacattt aaaatctact ctgttagcaa ttttgaagta tagaatacac tatgtcaact 600
ataatcatgg tgttgtacag taggtctaaa tgtattcatt tctcctatct aactgaaaat 660
ttgtatcttt tgaccaacat ctccctgggc cctccatctc ctccctggg aactaccatt 720
attttttttt ctttttttta aaaaaaagct tttagtttcg agggtagacg tgtaggtttg 780
ttatatagat aaacncaagt catgggactg tgttgtacag attattttgt cgtccacgta 840
ctaagcctag tgcccaatag ttattttttt tgctcttctc cctcctccta ccctctgcca 900
tcaagttggc ctaatgtcta ttgttccctt ctttgaaca accactctaa tctctgcttc 960
taagggttcc tatgtctgac ttctttccct tgattttgtg agattcatcc acgttgtgta 1020
tgcagcagta gtttattttat ttccattatt ggatagtatt cctttgtgtg aacataaatt 1080
gctgatggca gatgtttgaa ttgtttccag tttttgagta ttatgaataa tgctgttgtg 1140
aacaaaaaaaa aaaaaaaaaa aaaaaaaggg cggccgctct agaggatcca agcttgcgta 1200
cgcgtgcatg aaacgtcana agggctctnn n 1231

```

<210> 247

<211> 851

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (817)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (842)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (844)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (849)

<223> n equals a,t,g, or c

<400> 247

gcggacgcgt gggcgtggat cggctggagc ggggccgccg ccggctgcag caggagctgg 60

155

```

acgacgccac catggacctg gagcagcagc ggcagcttgt gagcaccctg gagaagaagc 120
agcgcaagtt tgaccagctt ctggcagagg agaaggcagc tgtacttcgg gcagtggagg 180
aacgtgagcg ggccgaggca gagggccggg agcgtgaggc tcgggccctg tactgacac 240
gggcactgga ggargagcag gaggcacgtg aggagctgga gcggcagaac cgggccctgc 300
ggctgagctg gaggcactgc tgagcagcaa ggatgacgtc ggcaagagcg tgcatgarct 360
ggaacgagcc tgccgggtag cagaacaggc agccaatgat ctgcgagcac aggtgacaga 420
actggaggat gagctgacag cggccgagga tgccaagctg cgtctggagg tgactgtgca 480
ggctctcaag actcagcatg agcgtgacct gcagggccgt gatgaggctg gtgaagagag 540
gcggaggcag ctggccaagc agctgagaga tgcagaggct gagcgggatg aggagcggaa 600
gcagcgcact ctggccgtgg ctgcccgcaa gaagctggag ggagagctgg aggagctgaa 660
ggctcagatg gcctctgccg gccagggcaa ggaggaggcg gtgaagcagc ttcgcaagat 720
gcaggcccag atgaaggagc tatggcggga ggtggaggag acacgcacct tccgggagga 780
gatcttctcc cagaatcggg aaagtgaana gcgcctnaag ggcctgaagc tgangtgctg 840
cngntgcang a 851

```

<210> 248

<211> 1802

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1680)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1747)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1757)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1800)

<223> n equals a,t,g, or c

<400> 248

```

acgcgtccgc ttocatctgc tctggaatta aatatgcatt tcaggtgatt ggagagctac 60
attcccaact cgatggatcc gaagtactgc tgctgactga tggggaggat aacactgcaa 120
gttcttgtat tgatgaagtg aaacaaagtg gggccattgt tcattttatt gctttgggaa 180
gagctgctga tgaagcagta atagagatga gcaagataac aggaggaagt catttttatg 240
tttcagatga agctcagaac aatggcctca ttgatgcttt tggggctytt acatcaggaa 300
atactgatct ctccsagaag tcccttcagc tcgaaagtaa gggattaaca ctgaatagta 360
atgcctggat gaacgacact gtcataattg atagtacagt gggaaaggac acgttctttc 420
tcatacatg gaacagtctg cctcccagta tttctctytg ggatcccagt ggaacaataa 480
tggaaaattt cacagtggat gcaacttcca aaatggccta tctyagtatt ccaggaactg 540
saaaggtggg cacttgggca tacaatctty aagccaaagc gamcccagaa acmttaacta 600

```

156

```

ttacagtwac ttctcgagca kcaaaattct tctgtgcctc caatcacagt gaatgctaaa 660
atgaataagg acgtaaacag tttccccagc ccaatgattg tttacgcaga aattctacaa 720
ggatatgtac ctgttcttgg agccaatgtg actgctttca ttgaatcaca gaatggacat 780
acagaagttt tggaactttt ggataatggg gcaggcgctg attctttcaa gaatgatgga 840
gtctactcca ggtatttttac agcatatata gaaaatggca gatatagctt aaaagttcgg 900
gctcatggag gagcaaacac tgccaggcta aaattacggc ctccactgaa tagagccgcy 960
tacataccag gctgggtagt gaacggggaa attgaagcaa acccgccaag acctgaaatt 1020
gatgaggata ctcagaccac cttggaggat ttcagccgaa cagcatccgg aggtkcattt 1080
gtggtatcac aagtcccaag ctttcttgc ctgaccaata cccaccaagt caaatcacag 1140
accttgatgc cacagttcat gaggataaga ttattcttac atggacagca ccaggagata 1200
attttgatgt tggaaaagtt caacgktata tyataagaat aagtgcaagt attcttgatc 1260
taagagacag ttttgatgat gctcttcaag taaatactac tgatctgtca ccaaaggagg 1320
ccaactccaa ggaaagcttt gcattttaa cagaaaatat ctcagaagaa aatgcaaccc 1380
acatatatat tgccattaaa agtatagata aaagcaattt gacatcaaaa gtatccaaca 1440
ttgcacaagt aactttgytt atccctcaag caaatcctga tgacattgat cctactccta 1500
ctcctactcc tactcctgat aaaagtcata attctggagt taatatttct acgctgggtat 1560
tgtctgtgat tgggtctggt gkaattgkta actttatttt aagtaccacc atttgaacct 1620
taacgaagaa aaaaatcttc aagtagacct agaagagagt tttaaaaaac aaaacaatgn 1680
aagtaaagga tatttctgaa tcttaaaatt catcccatgt gtgatcataa actcataaaa 1740
ataattntaa gatgtcngga aaaggatact ttgattaaaa taaaaacact catggatatn 1800
ta 1802

```

<210> 249

<211> 444

<212> DNA

<213> Homo sapiens

<400> 249

```

gggtgccttt ctcatggcca cagcagcttg gcttacaacc gtcttcaaac agccaggctg 60
tgccccagaa ctactctggg ctctcttcca taactatgga tctgtgagca tcactttaat 120
ttcagagtggt ggaagacacc ttaataagaa tcatgaatca cattttacaa atcaggatac 180
acaggatgta aggttaagtg acctgtccta tcaggggccac aaagccagtt aaacttcttt 240
attaactgag tcaacttaaaa atcatttatt taaaaaccta ttttgttcca ggaactattc 300
tgggtactgg aaatrraaac agtggagaca gagagagggg aaatpaaaaa caagacaaaa 360
atgattgctt tkgtggagtt tatatatctc actggargaa ggtagatsat aaataaaagt 420
gaaaaagtac attatwaggt ggga 444

```

<210> 250

<211> 1746

<212> DNA

<213> Homo sapiens

<400> 250

```

ggcatcagta aggtctgtat ttaaattgtg atgtagacat cataattacc aagacaagaa 60
attgttttga gaaattctct gatgtttttc ttcttcagggt ttcacgtgcc acgatcatgg 120
tgccacggta ctgcagtatg caccctaaaca gcaactccta atctcggggg gtaggaaaag 180
acacgtctgc atttttgaca tcargcaaaag gcagctcatt cacacgttcc aggcccatga 240
ctcagctatt aaggctctgg ccttggatcc ctatgaggaa tattttacca caggttcagc 300
agaaggtaac ataaagggtt ggagattgac aggccatggc ctaattcatt catttaaaag 360
tgaacatgct aagcagtcca tatttcgaaa cattgggggt ggagtcatgc agattgacat 420
catccagggc aatcggtctt tctcctgtgg tgcagatggc acgctgaaaa ccagggtttt 480

```

157

```

gcccaatgct ttttaacatcc ctaacagaat tcttgacatt ctataaagat tgggggtttta 540
tttttatata catttcagtt aaaaggcaca ctacagtcac cactaggcaa ttctgctttc 600
taagcagttg tattgaaaac agagaatctc tgtgtagaat ttgaatatga cccaagctga 660
gtattatcta aacaggttgg tggaaatgaat gcgcagtgtac cttattatgc tgacatacta 720
aaaaaaataa aacctagtat tgtatgaagg atagctattc tttacagcat ttagcaaacc 780
tgattcagaa aacatttgag attagcaaat tagtaacttg aaataatgaa aaggacgttt 840
ataccaaatt aaggaagaaa atgttgctga tttgggtttt tcttcctgtt cttaccactg 900
actgaagcat gcctgcagtc tctcctctctg ttgaatgaag gataatcata aggtgtttgt 960
taggagcgct agaccacctg gaaaactttc ttagctgtgg agcagtgcgc agtgaccagt 1020
tctctgctgt gagaggcctg ttccattctt tctgtgtgaa tatttttctt gttagtgttt 1080
atactgagct agtactgtaa cttgcaaatt agtgcaaatt taaatgcaat gttttactca 1140
caatttgcac attcacattt tttggactgc tagtttttct atttaaatat ttgccttcat 1200
gttaggaatg tactatgtga acatgacata tttgtagtta accaaacaca ccttcttagt 1260
ccagtttagt actttttctt ttcgtgtatt caagggttaa caccacaaca tttaaggata 1320
tgttgaaact acaccaatag agcatttcat atcataatta aaatgaatgt taggcttctt 1380
gtggccagtt aatagttgat gagattggtg acattattta ttgccacagc ctattgtata 1440
aactatgcag agttaaatat ttgcttgtaa aatattagcc aatgttgtca ttattttgat 1500
gtatttctct ggttatgacc aaaaatatgt tgagatactg aaactaatgt ctgtgtgttt 1560
aatgtttac cagcaaattg tcttatcatg ttaatgagaa tgttcaatgc ctgtgtggtg 1620
aatagtaaat acaatggcat aaaagtaact ttctctgaag atgtgatgtt caggctgtga 1680
aatatatatg taaaagaaaa ataaatgtta tttgttagaa aaaaaaaaaa aaaaaaaaaa 1740
ctcgta 1746

```

<210> 251

<211> 1935

<212> DNA

<213> Homo sapiens

<400> 251

```

gaattcggca cgaggaggca ttgcccgtca gacagcaact cagagaataa ccagagaaca 60
accagattga aacaatggag gatctttgtg tggcaaacac actctttgcc ctcaatttat 120
tcaagcatct ggcaaaagca agccccaccc agaacctctt cctctcccca tggagcatct 180
cgtccaccat ggccatggtc tacatgggct ccaggggcag caccgaagac cagatggcca 240
aggtgcttca gtttaatgaa gtgggagcca atgcagttac ccccatgact ccagagaact 300
ttaccagctg tgggttcatg cagcagatcc agaagggtag ttatcctgat gcgattttgc 360
aggcacaagc tgcagataaa atccattcat ccttccgctc tctcagctct gcaatcaatg 420
catccacagg gaattattta ctggaaagtg tcaataagct gtttggtgag aagtctgcga 480
gcttccggga agaataatatt cgactctgtc agaaatatta ctctcagaa cccagggcag 540
tagacttcct agaatgtgca gaagaagcta gaaaaaagat taattcctgg gtcaagactc 600
aaaccaaagg caaaatccca aacttgttac ctgaagggtc tgtagatggg gataccagga 660
tggctcctgg gaatgctgtc tacttcaaag gaaagtggaa aactccattt gagaagaaac 720
taaatgggct ttatcctttc cgtgtaaaact cggctcagcg cacacctgta cagatgatgt 780
acttgcggtg aaagctaaac attggatata tagaagacct aaaggctcag attctagaac 840
tcccatatgc tggagatgtt agcatgttct tgttgcttcc agatgaaatt gccgatgtgt 900
ccactggctt ggagctgctg gaaagtgaat taacctatga caaactcaac aagtggacca 960
gcaaagacaa aatggctgaa gatgaagttg aggtatacat accccagttc aaattagaag 1020
agcattatga actcagatcc attctgagaa gcatgggcat ggaggacgcc ttcaacaagg 1080
gacggggcaa tttctcaggg atgtcggaga ggaatgacct gtttctttct gaagtgttcc 1140
accaagccat ggtggatgtg aatgaggagg gcaactgaag agccgctggc acaggaggtg 1200
ttatgacagg gagaactgga catggaggcc cacagtttgt ggcagatcat ccttttcttt 1260
ttcttattat gcataagata accaactgca ttttattttt cggcagattt tctcaccct 1320

```

158

```

aaaactaagc gtgctgcttc tgcaaaagat ttttgtagat gagctgtgtg cctcagaatt 1380
gctatttcaa attgccaaaa atttagagat gttttctaca ttttctgct cttctgaaca 1440
acttctgcta cccactaaat aaaaacacag aaataattag acaattgtct attataacat 1500
gacaacccta ttaatcattt ggtcttctaa aatgggatca tgcccattta gattttcctt 1560
actatcagtt tttttttata acattaaact ttactttggt atttattatt ttatataatg 1620
gtgagttttt aaattattgc tctactgccta tttaatgtag ctaataaagt tatagaagca 1680
gatgatctgt taatttccta tctaataaat gcctttaatt gttctcataa tgaagaataa 1740
gtaggtatcc ctccatgccc ttctgtaata aatatctgga aaaaacatta aacaataggc 1800
aaatatatgt tatgtgcatt tctagaaata cataacacat atatatgtct gtatcttata 1860
ttcaattgca agtatataat aaataaacct gcttccaaac aacaaaaaaaa aaaaaaaaaa 1920
aactttgagg gggggg                                     1935

```

<210> 252

<211> 1919

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (253)

<223> n equals a,t,g, or c

<400> 252

```

ataaggcggc atttatcatt cccaccactg acatctactg tataccacat ctgctatgcc 60
atggatacat ggcacatga tgatgagtc cccccctggg cctgccaagg ggaaacagag 120
tgcatatccc accataatag ggaaattaat aattgtatta agtggttgaa aaaaaggggg 180
aggatgttca ctactgttc cctgtgtagt atcctgcaaa tgcataaatg gtgaactccc 240
catgtcagca ttnttggtgc catttattta gtaccagac atagtgtgtg tctcacagct 300
taatatttgg taatgaataa attctgctag tggatatgt tgatctgaac ttacaatgat 360
gggatataga attggcagag tggcagatgt tcacaattgt ctacaagtag atgtgctaga 420
caatggaagg atgcaggcca acctcttga ttacaattga gattcatgtg actattgagc 480
cctggaaaatg tagcttgtcc aaattgagat gtgctgtcag tataaaatac ataccagatt 540
ttaaagatgt accaaaaaat gtaaaactat tcaattttta tattggtgaa atcaatatgt 600
cttgggtatag tggcttaaat aaaacaattt tagcctttct cagtttattt ttctgcaaaa 660
agattaaaaa ttgtacatga agctcatgtt aactttcttt tggtcagtgc ttttttaaag 720
gaagtatgag ttgaaaaaaa attgaaataa actatatcat attactagga cttaatatag 780
tggcataccc aggaaatgct tagtaagtgt tcccttcaca ttttaaaatt tgagtataca 840
atcatgtttg acaatataga aatttaattt ttagtgaac aattctaaac ccttttcca 900
tagacacaag aaagatggca aatttatgct attcctggaa aaatacattg tggcttagca 960
aataagcaag tccccacgtt acttttgttt tgcttcaagt aatacttctg ccagttgtgt 1020
tttatgaatt aaacagggaa cggcatgctg aacttgaaac tagatttgtt cctgcttttt 1080
tcacaatgtg agtagttttg aaaagtcaga tctggccatt tgtctttcct agaatagcac 1140
aactttgttc attgtttttt ttgtttgtct ttctgacaca gaaagactga tgatggtgtc 1200
cactatgtat tcttcaaaac atttggcaca tgctgcacta acctagtcta tcttttctat 1260
cttgggaattt gctcatacaa accctatagc ctagactaga tcccttacct tctctccagt 1320
tcctatcatt caccattttc actgtgcaag acacctcact agtcaccagt gatacagaaa 1380
tgacttttaa gcagtttctg ctcttaaggg cttaccgttt tgtctataag atacacaagt 1440
ataaatgaca agtacaaata acaatgaatg tttaatgctt tacgttttagt gtttaagctt 1500
gttgttgtaa gagcagcatt ttgacccttg gagaagaaaa actagctgtg gcattccagg 1560
tggagaacct gacagaggac taagaagtta tctaattgaa aagacctcag gcaccacctt 1620
cgcataaact ttttccagac aaggctaaat gtgcatgctt cataaccata attcttattt 1680

```

159

```

ttctttaata aatatttttc tacttgtaac actgtgcatt atttcaaact gtttacctgt 1740
ttgtaaagct tgtctcttaa tcaaatttgt cttgacccaa taagtttcct gagggctgga 1800
attatgcctt aactatatct atagtattta acagtgaatc ctttgtataa tgaaagcatc 1860
aacagataat tttaaattga taaataaaaa gcacagtttc aaatggtaaa aaaaaaaaaa 1919

```

<210> 253

<211> 2468

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2076)

<223> n equals a,t,g, or c

<400> 253

```

gggttttgaga agattggaca gtgcttcagg caccgtgtac acagcaatgg atgtggccac 60
aggacaggag gtggccatta agcagatgaa tcttcagcag cagcccaaga aagagctgat 120
tattaatgag atcctggtca tgagggaaaa caagaaccca aacattgtga attacttgga 180
cagttacctc gtgggagatg agctgtgggt tgttatggaa tacttggtg gaggcctcct 240
gacagatgtg gtgacagaaa cttgcatgga tgaaggccaa attgcagctg tgtgccgtga 300
gtktctgcag gctctggagt tcttgcatte gaaccagata accccagagc agagcaaacg 360
gagcaccatg gtaggaaccc catactggat ggcaccagag gttgtgacac gaaaggccta 420
tgggcccagg gttgacatct ggtccctggg catcatggcc atcgaaatga ttgaagggga 480
gcctccatac ctcaatgaaa accctctgag agccttgtac ctcatcgcca ccaatgggac 540
cccagaactt cagaaccagc agaagctgtc agctatcttc cgggactttc tgaaccgctg 600
tctcgagatg gatgtggaga agagagggtc agctaaagag ctgctacagc atcaattcct 660
gaagattgcc aagccctctc ccagcctcac tccactgatt gctgcagcta aggaggcaac 720
aaagaacaat cactaaaacc acactcacc cagcctcatt gtgccaagcc ttctgtgaga 780
taaatgcaca tttcagaaat tccaactcct gatgccctct tctccttgcc ttgcttctcc 840
catttcctga tctagcactc ctcaagactt tgatccttgg aaaccgtgtg tccagcattg 900
aagagaactg caactgaatg actaatcaga tgatggccat ttctaaataa ggaatttcct 960
cccaattcat ggatatgagg gtggtttatg attaaggggt tatataaata aatgtttcta 1020
gtcttccgtg tgtcaaaatc ctcaacctct tcataacat ctcaccacat taattcctga 1080
ctatataaat ttatggtttg ataataatt caatttgtaa tcaattgaga ttctcttagt 1140
gcttgctttt ctgtgactca actgccaga cacctcattg tacttgaaaa ctggaacagc 1200
ttgggaatgc catgggggtt gataatctgc caggagacatg aagaggctca gcttcctgga 1260
ccatgacttt ggctcagctg atcctgacat gggagaacaa ccacattttt ctttgtgtgt 1320
gcttctagca gctgttcggg aggaccttga cccaayagtg tccccatgct gtttcttgtg 1380
aaatgctctc ggctatgtag cagcttttga ttccctgcat accctaggct gctgccccta 1440
tcctgtccct tgtttataac attgagagggt tttctagggc acatactgag tgagagcagt 1500
gttgagaagt cgggggaaat ggtgactact tttagagcaa ggctgggcat cagcacctgt 1560
ccagctctac ttgtgtgatg tttcaggaac tcagccccct tttctgccta ggataaggag 1620
ctgaaagatt aacttggatc ttctaattgg ccaaatcttt tggtcacaat aaagagtctc 1680
caaattagag actgcatgtt agttctggat ggatttgggt gcctgacatg ataccttgc 1740
agctgtgagg ggacccccgt ttttaagatgc atggccaagc tctctgcaa tggaaatgct 1800
tacactgggt gttggggatg tttgctacct cctgctatatt ttgtgggttt gggttctcca 1860
ctatggtagg acccctggcc agcattgtgg cttgtcatgt cagccccatt gactaccttc 1920
tcatgctctg aggtactact gcctctgcag cacaaatttc tatttctgtc aataaaagga 1980
gatgaaaata ttctattgga gtatgccttt cttttttctc ttcgtttttt ctttcctttt 2040
ctaatttttt atatgaaata atgagtaagt ttcttntctga accatttgag agtggttaagt 2100

```

160

```

tgcagataga atgcccccttt accactatat acctgaatgt gtattctttc yttttaacac 2160
ttttatttta aatataaatt aagagaaatg ggccaaaacc atttgtattg tttaaagaat 2220
aattataaac acacttgtat ccaccaaate aagaaakgga aactgacag taagaacctt 2280
ctctatcttg tccttccttt ctctattatag cccccaccta agaggtaacc accatcttga 2340
cttttatttta aataactttc ttgctttttc gtatactttc atcacattca ggtgtgttcc 2400
aatacaagta gatttttagtt cggccagttt ttgaacttta aataaacata tcataataga 2460
taaaaaaa

```

<210> 254

<211> 2861

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2861)

<223> n equals a,t,g, or c

<400> 254

```

ggcacarca cagcttctcc agtggctatg tggagatgga gtttgagttt gaccggctga 60
gggccttcca ggctatgcag gtccactgta acaacatgca cacgctggga gcccgctctgc 120
ctggcggggt ggaatgtcgc ttccggcgctg gccctgccat ggccctgggag ggggagccca 180
tgcgccacaa cctaggggggc aacctggggg accccagagc cggggctgtc tcagtgtccc 240
ttggcgggcg tgtggctcgc tttctgcagt gccgttctct ctttgcgggg ccctgggttac 300
tcttcagcga aatctccttc atctctgatg tggatgaaca ttctctctcg gcaactgggag 360
gcaccttccc gccagccccc tgggtggccgc ctggcccacc tcccaccaac ttcagcagct 420
tggagctgga gccagagggc cagcagcccg tggccaaggc cgagggggagc ccgaccgcca 480
tcctcatcgg ctgectgggtg gccatcatcc tgcctctgct gctcatcatt gccctcatgc 540
tctggcgggct gcaactgggc aggytcctca gcaaggytga acggagggtg ttggaagagg 600
agctgacggg tcacctctct gtccctgggg acactatctt catcaacaac cgcccagggtc 660
ctagagagcc acccccgtag caggagcccc ggccctcgtag gaatccggcc cactcygctc 720
cctgtgtccc caatggctct gcgttgcctg tctccaatcc agcctaccgc ctcttctctg 780
ccacttacgc ccgtcccccct cgaggccccg gccccccac acccgccctg gccaaaccca 840
ccaacaccca ggccctacagt ggggactata tggagcctga gaagccaggc gcccgccttc 900
tgccccacc tcccagaac agcgtccccc attatgccga ggctgacatt gttaccctgc 960
agggcggtcac cgggggcaac acctatgctg tgccctgact gccccagggt gcactcgggg 1020
atgggcccc cagagtggat ttccctcgat ctgcactccg cttcaaggag aagcttggcg 1080
agggccagtt tggggagggtg cacctgtgtg aggtcgacag ccctcaagat ctggctcagtc 1140
ttgatttccc ccttaatgtg cgtaaggagc accctttgct ggtagctgtc aagatcttac 1200
ggccagatgc caccaagaat gccaggaatg atttcttgaa agagggtgaag atcatgtcga 1260
ggctcaagga cccaaacatc attcggctgc tgggcgtgtg tgtgcaggac gacccctct 1320
gcatgattac tgactacatg gagaacggcg acctcaacca gttcctcagt gccaccagc 1380
tggaggacaa ggcagccgag gggggccctg gggacgggca ggctgcgcag gggccacca 1440
tcagctaccc aatgctgctg catgtggcag ccagatcgc ctccggcatg cgctatcttg 1500
ccacactcaa ctttgtacat cgggacctgg ccacgcggaa ctgcctagtt ggggaaaatt 1560
tcacatcaa aatcgagac tttggcatga gccggaacct ctatgctggg gactattacc 1620
gtgtgcaggg ccgggcagtg ctgccatcc gctggatggc ctgggagtg atcctcatgg 1680
ggaagtac gactgcgagt gacgtgtggg ctttgggtgt gaccctgtgg gaggtgtga 1740
tgctctgtag ggcccagccc tttgggcagc taccgcagca gcagggtcatc gagaacgcgg 1800
gggagttctt ccgggaccag ggccggcagg tgtacctgtc ccggccgcct gcctgcccgc 1860
aggcytatat gagctgatgc ttcgggtgctg gagccgggag tctgagcagc gaccaccctt 1920

```

161

```

ttcccagctg catcggttcc tggcagagga tgcactcaac acggtgtgaa tcacacatcc 1980
agctgccccct ccttcaggga gcgatccagg ggaagccagt gacactaaaa caagaggaca 2040
caatggcacc tctgcccttc cctccccgac agcccatcac ctctaataga ggcagtgaga 2100
ctgcagggtgg gctgggcccc cccagggagc tgatgccctt tctccccctc ctggacacac 2160
tctcatgtcc ctttctgttt cttccttctt agaagcccc ttcgcccacc cagctggtcc 2220
tgtggatggg atcctctcca cctcctctta gccatccctt ggggaagggg ggggagaaat 2280
ataggataga cactggacat ggcccattgg agcacctggg cccactgga caacactgat 2340
tcctggagag gtggctgcgc ccccagcttc tctctccctg tcacacactg gacccactg 2400
gctgagaatc tgggggtgag gaggacaaga aggagaggaa aatgtttcct tgtgcctgct 2460
cctgtacttg tctcagctt gggctttctt cctctccatc acctgaaaca ctggacctgg 2520
gggtagcccc gccccagccc tcagtcaccc ccacttccca cttgcagtct tgtagctaga 2580
actttctctaa gcctatacgt ttctgtggag taaatattgg gattgggggg aaagaggagg 2640
caacggccca tagccttggg gttggacatc tctagtgtag ctgccacatt gatttttcta 2700
taatcacttg gggtttgtac atttttgggg ggagagacac agatttttac actaatatat 2760
ggacctagct tgaggcaatt ttaatccctt gcaactaggca ggtaataata aagggtgagt 2820
tttccacaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa n 2861

```

<210> 255

<211> 766

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (107)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (709)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (722)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (732)

<223> n equals a,t,g, or c

<400> 255

```

aaaggggggtc gagtaactca agtgttagaa gttcggtgac ttttgactgg ggagaaagga 60
accttaaaact tggggaggag aaggaggatc tggagttggt acctanaaac aaagatgggg 120
cggaatggag gctacagccc gaaagccagg ccagcagtgg cgttcttctg tgtccccaag 180
tagtggactt gagcccgtcg agacctcggc aggagtctcg tcccagggca ggtgggtgtg 240
cggggtgagc cgcgagcgcg ttccagctcg ggtaaagagg aagttacctc gggtcctttg 300
cactccaaact cggcggcgcg cgagcccagc gggccccagc caaccgcagc cccgtgtgtt 360
gtgtgtgtct aacacccggg ccgtgcgcgc gccgcgcgcg ccgcgctgcc cccagctcga 420
ggaggacatc gcggccaagg agaagttgct gcgggtgtcg gaggacgagc gggaccgggt 480

```

162

```

gctggaggag ctgcacaagg cggaggacag cctcctggcc gccgaagagg ccgcgcccaag 540
gctgaagccc gacgtagctt ctctgaacag acgcatccag ctggttgagg aagagttgga 600
tcgtgcccag gagcgtcttg caacagcttt gcagaagctg gaggaagctg ataaggcagc 660
agatgagagt gagagaggca tgaaagtcac tgagagtcga gccc aaaang gatgaagaaa 720
anatggaaat ttaggagatc caactgaaag aggcaaagca cattgc 766

```

<210> 256

<211> 1394

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1238)

<223> n equals a,t,g, or c

<400> 256

```

gcccacgcgt ccgagctcag tcagcagaag agataaaagc aaacaggtct gggaggcagt 60
tctgttgcca ctctctctcc tgtcaatgat ggatctcaga aataccccag ccaaattctt 120
ggacaagttc attgaagact atctcttgcc agacacgtgt ttccgcatgc aaatcaacca 180
tgccattgac atcatctgtg ggttcctgaa ggaaaggtgc ttccgaggta gctcctaccc 240
tgtgtgtgtg tccaaggtgg taaaggtgg ctctcaggc aagggcacca cctcagagg 300
ccgatctgac gctgacctgg ttgtcttctc cagtcctctc accacttttc aggatcagtt 360
aaatcgccgg ggagagttca tccaggaaat taggagacag ctggaagcct gtcaaagaga 420
gagagcattt tccgtgaagt ttgaggtcca ggctccacgc tggggcaacc cccgtgcgt 480
cagcttcgta ctgagttcgc tccagctcgg ggagggggtk gaggttcgat tgctgectgc 540
ctttgatgcc ctggattttg cccgwacagg tcaattgact ggcggtata aacctaaccc 600
ccaaattctat gtcaagctca tcgaggagt caccgacctg cagaaagagg gcgagttctc 660
cacctgcttc acagaactac agagagactt cctgaagcag cgccccacca agctcaagag 720
cctcatccgc ctagtcaagc actggtacca aaattgtaag aagaagcttg ggaagctgcc 780
acctcagtat gccctggagc tcctgacggt ctatgcttg ggcgaggga gcatgaaaac 840
acatttcaac acagcccagg gatttcggac ggtcttgga ttagtcataa actaccagca 900
actctgcac tactggacaa agtattatga ctttaaaaac cccattattg aaaagtacct 960
gagaaggcag ctacgaaac ccaggcctgt gatcctggac ccggcggacc ctacaggaaa 1020
cttgggtggg ggagacccaa agggttggag gcagctggca caagargctg aggcctggct 1080
gaattaccca tgctttaaga attgggatgg gtccccagtg agctcctgga ttctgctgg 1140
gagacctcct gcttctctcc tgccattcat cctgccccct ctccatgaag cttgagacat 1200
atagctggag accattcttt ccaaagaact tacctctntc gcaaaggcca tttatattca 1260
tatagtgaca ggctgtgctc catattttac agtcattttg gtcacaatcg agggttctc 1320
gaattttcac atccctgtgc cagaattcat tcccctaaga gtaataataa ataattctc 1380
acacccaaaa aaaa 1394

```

<210> 257

<211> 1329

<212> DNA

<213> Homo sapiens

<400> 257

```

ctcatcctca acctggtgac agacttgaag cccagatgc tgttggacac agtgcctgt 60
atccccgct acatcctcta catgtgcac cggctcgcg accaaacca tgatgatctc 120
aagtgcmct cctgmtgac ctccaccayc aacggcata agraagtc gaaraagcac 180

```


163

```

artgatgact ttgagatgac gtcattctkg ttatccaaca cctgccacct tcttcaactgt 240
ctgaagcggg acagcgggga tgaggggcttc atgactcaga atacwgcaaa gcacaacgaa 300
cactgyctta agaaytttga cctcaccgaa taccgtcagt actgagcgac ctttccattc 360
agatctacca gcagctcwtt aaaattgccg aggggygygtt acagccgatg atagtttctg 420
ccatgttggg aatgagagc attcaggggtc tatctggtgt gaagcccacy ggctmccrga 480
agcrctcctc cagcatggca gatggggata actcatacyg cctggaagct wtcateccgc 540
agatgaatgc ctttcataca gtcattgtgt accagggctt ggaccctgag atcatectgc 600
aggtattcaa acagctcttc tacatgatca acgcagtgc tcttaacaac ctgctcttgc 660
ggaaggacgt ctgctcttgg agcacaggca tgcaactcag gtacaatata agtcagcttg 720
aggagtggct tcggggaaga aaccttcacc agagtggagc agttcagacc atggaacctc 780
tgatccaagc agcccagctc ctgcaattaa agaagaaaac ccaggaggac gcagaggcta 840
tctgctccct gtgtacctcc ctccagcccc agcagattgt caaaatttta aacctttata 900
ctcccctgaa tgaatttgaa gaacgggtaa cagtggcctt tatacgaaca atccaggcac 960
aactacaaga gcggaatgac cctcagcaac tgctattaga tgccaagcac atgtttcctg 1020
ttttgtttcc atttaatcca tcttctctaa ccatggactc aatccacatc ccagcgtgtc 1080
tcaatctgga attcctcaat gaagtctgaa gatgcatgtt tccagcatta gtttgattcc 1140
caatgtgagc aagaaggaag tatatacagt aaagtaaatt caaggatctg ttaaactctg 1200
taaaagtaga tcaaatcaga gattgacagc ctgtggaggg tgctgaacta tacagaatta 1260
gacacaacta tgtcattatt ttttgtacct actgctcaga ataaaaaacac ttgaaatatg 1320
aaaaaaaaa                                     1329

```

<210> 258

<211> 2196

<212> DNA

<213> Homo sapiens

<400> 258

```

aattcggcag agcgggaagt cgctgaagac agagcgatgg tagttctgga ggccctcgctc 60
cggggccgac ccgaggccac agtgccctcg cggtagaccg gacttgggtg acgggctccg 120
ggctcccag gtgaagagca tcgggggctg agggatggaa gggctctaaga cgtccaacaa 180
cagcaccatg caggtgagct tcgtgtgcca gcgctgcagc cagccccctga aactggacac 240
gagtttcaag atcctggacc gtgtcaccat ccaggaactc acagctccat tacttaccac 300
agcccaggcg aaaccaggag agaccagga ggaagagact aactcaggag aggagccatt 360
tattgaaact cctcgccagg atggtgtctc tcgcagattc atccccccag ccaggatgat 420
gtccacagaa agtgccaaca gcttcaactc gattggggag gcatctgatg gcggcaccat 480
ggagaacctc agccgaagac tgaaggtcac tggggacctt tttgacatca tgtcgggcca 540
gacagatgtg gatcacccac tctgtgagga atgcacagat actcttttag accagctgga 600
cactcagctc aacgtcactg aaaatgagtg tcagaactac aaacgctgtt tggagatctt 660
agagcaaatg aatgaggatg acagtgaaca gttacagatg gagctaaagg agctggcact 720
agaggaggag aggtgatcc aggagctgga agacgtggaa aagaaccgca agatagtggc 780
agaaaatctc gagaagggtc aggtgagggc tgagagactg gatcaggagg aagctcagta 840
tcagagagaa tacagtgaat ttaaaccgaca gcagctggag ctggatgatg agctgaagag 900
tgttgaaaac cagatgcgtt atgcccagac gcagctggat aagctgaaga aaaccaacgt 960
ctttaatgca accttccaca tctggcacag tggacagttt ggcacaatca ataacttcag 1020
gctgggtcgc ctgcccagtg ttcccgtgga atggaatgag attaatgctg cttggggcca 1080
gactgtgttg ctgctccatg ctctggccaa taagatgggt ctgaaatttc agagataccg 1140
acttgttcct tacggaaacc attcatatct ggagtctctg acagacaaat ctaaggagct 1200
gccgttatac tgttctgggg gggtgcggtt tttctgggac aacaagtttg accatgcaat 1260
ggkggctttc ctggactgtg tgcagcagtt caaagaagag gttgagaaaag gcgagacacg 1320
tttttgtctt ccctacagga tggatgtgga gaaaggcaag attgaagaca caggaggcag 1380
tggcggctcc tattccatca aaaccagtt taactctgag gagcagtgga caaaagctct 1440

```

164

```

caagttcatg ctgacgaatc ttaagtgggg tcttgcttgg gtgtcctcac aattttataa 1500
caaatgactt ttttccttag ggggaggttt gccttaaagg cttttaattt tgttttgttt 1560
gcaaacatgt tttaaattaa attcgggtaa tattaaacag tacatgttta caataccaaa 1620
aaagaaaaaa tccacaaaag ccactttatt ttaaaatata atgtgacaga tactttccag 1680
agctacaaca tgccatctat agttgccagc cctggtcagt tttgattctt aaccccatgg 1740
actcctttcc ctttcttctc tgaaaaaaac taatttaaata ttgcttttct tttttttaac 1800
tgagttgaat tgagattgat gtgttttcac tggattttta tctctctcaa cttcctgcac 1860
ttaacaatat gaaatagaaa cttttgtctt tactgagatg aggatatgtt tgagatgcac 1920
agttggataa tgtgggaaaa tgacatctaa gctttacctg gtcaccatgt gatgtgatca 1980
gatgcttgaa atttaacact tttcacttgg ttcttatact gaatgccgac tctgctctgt 2040
gttagagata tgaaatggtg tttgatactg tttgagacat tatggagaga ttttaattatt 2100
tgtaataaaa gatttgctgc agtctgaaaa ctgcccaggg gtgcactgtt ggggttttct 2160
ttaaaataga gtactttgta ttctgggaaa aaaaaa 2196

```

<210> 259

<211> 567

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (236)

<223> n equals a,t,g, or c

<400> 259

```

gtttacataa gagatccctt agtccactca acggctgaca ttagcagcat ctttaataca 60
actgtttgtt caaaggcaag gtggtccctt ttaaagttac acttctagac tcacctgttc 120
tcaactccctg ttttaatgta acccagccat gagatgccag ataatagaat tgctacctac 180
tagctgaaca ggaaagaacc tgtgctgttt ctgacacttc ttgttgaca tagatnaata 240
caatgggtat tatagagact cagttgcaga aattaacaaa catgctgctt ggttaaaatg 300
ggtagactca tctggctcat tctttattcc attttagttg gtttgcatct tgcctaagggt 360
gcatactcca aactyttggt attattctcc tgatagtcac actagtagtc tccctggtgt 420
gtataaatct ctaaaagctt taaatgtttg cwtgcagcta tccatcgaat gtcaaatggt 480
ctctcttttg ctggaatgac aaaactcaaa ggaatgtgtg atcaggaaga catcataacc 540
tatgaatgat ggaacccaaa atgaatg 567

```

<210> 260

<211> 950

<212> DNA

<213> Homo sapiens

<400> 260

```

gactaatgaa ataactgttc actattgttg gttctacttg cagggttcag actaggcaat 60
gtggtacatg ctatacaggc aactgagcag agcattcatg ccactgacct ggtacctcgc 120
ttatgcttaa cattagccaa cctgaaccgt gtgatttatt tcatctgtga caccatcttc 180
tgggtgagga gcgtaggctc cacctctggc atcaacaaaag agaaatggcg aacgagggct 240
gtcaccact actactatcc tcttctgctg agccttgtea gggatctgta tgaaatctcc 300
ctgcagatga aacgagttac atgtgacagg gcaaagaaaag agaaatcagc atcccaggat 360
cctcttttgt tcagcgtggc tgaggaggwa acagaatggc tccaatcctt tctacttctt 420
ttattccgat ctctgaagca gcatactccc ttgctcctgg acacagtga gaacctttgt 480
gatatactga accctttgga cctgctgggg atctataaat ccaatcctgg catcattgga 540

```

165

```

cttggagggtc ttgtgtcctc tatagcaggc atgatcactg tggcatatcc tcagatgaag 600
ctgaagaccc gttagtgttt ttaggcttgg aactagtacc tactttaaaa gatggcctct 660
tggtgggaca gacatttgta taagtcacag gccatgtcat actgtgctta agttcttgtt 720
catgtgagca tttacaacc tgtgatgtgg gcagagatga ggccaagaac ggagaaggga 780
ggagcatgaa gagttgtatg tttttggagt gctggagtga cttgtgaatt tctgaatatt 840
ttcccttcat ctaacattga ttgaacatct cttatgtgca tagtgggagc ttagtatttg 900
ctgaatgaat aaaaattgaa aggaaaaaat ttaaaaaraa aaaaaaaaaa 950

```

<210> 261

<211> 475

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (444)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (451)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (454)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (470)

<223> n equals a,t,g, or c

<400> 261

```

caaagaattc ggcacgaggt ctgatcttcc tgcggctgaa ccgcccggct gagccgacat 60
tgccggcgtc ttggcgattc ggcccgaaga gctccgcttt cgctacagca tggtggccta 120
ctggagacag gctggactca gctacatccg atactcccag atctgtgcaa aagcagtgag 180
agatgcactg aagacagaat tcaaagcaaa tgctgagaag acttctggca gcaacgtaaa 240
aattgtgaaa gtaaagaagg aataatctac cctgactaaa gcttgaaatg ctacatttcc 300
aagggtgaaga tgtgtgggca catgttatgg cagattgaaa aggatctcat tccatgggaa 360
aaaaaaaaat cctgtcttgt tcataaattg acaatgtcaa taaattgaaa tatgggtcac 420
tgttaaaaaa aaaaaaaaaa aaangggggg ncnnttttaa agaatccaan ttac 475

```

<210> 262

<211> 1244

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1230)

166

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1232)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1235)

<223> n equals a,t,g, or c

<400> 262

```

ggcacgagga aagtactttt gctataagtt tcctaaaagt atttaatact tttttttttc 60
aathtagatt aaatctcttg atgaacagtg tgtggttggc aaaatttcca agcactggac 120
tggaattttg agagaggcat ttacagacgc tgataacttt ggaatccagt tccctttaga 180
ccttgatgtt aaaatgaaag ctgtaatgat tgggtgcctgt ttcttcattg acttcatgtt 240
ttttgaaagc actggcagcc aggaacaaaa atcaggagtg tggtagtgga ttagtgaaag 300
tctcctcagg aaatctgaag tctgtatatt gattgagact atctaaactc atacctgtat 360
gaattaagct gtaaggcctg tagctctggt tgtatacttt tgcttttcaa attatagttt 420
atcttctgta taactgattt ataaagggtt ttgtacattt ttttaatactc attgtcaatt 480
tgagaaaaag gacatatgag tttttgcatt tattaatgaa acttcctttg aaaaactgct 540
ttgaattatg atctctgatt cattgtccat ttactacca aatattaact aaggccttat 600
taatttttat ataaattata tcttgtccta ttaaacttag ttacaattta tttcatgcat 660
aagagctaag gttatttttg aaatgccata tattcaaaaa agctcaaaga taattttctt 720
tactattatg ttcaaataat attcaatatg catattatct ttaaaaagtt aaatgttttt 780
ttaatcttca agaaatcatg ctacacttaa ctctccttag aagctaactc ataccataat 840
attttcatat tcacaagata ttaaattacc aattttcaaa ttattgttag taaagaacaa 900
aatgattctc tcccaaagaa agacacattt taaatactcc ttactctaa aactctggta 960
ttataacttt tgaaagttaa tatttctaca tgaaatgttt agctcttaca ctctatcctt 1020
cctagaaaat ggtaattgag attactcaga tattaattaa atacaatatc atatatatat 1080
tcacagagta taaacctaaa taatgatcta ttagattcaa atatttgaaa taaaaacttg 1140
atttttttgt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaaaaaaa gggcgggccgn tntanaggat ccaa 1244

```

<210> 263

<211> 1132

<212> DNA

<213> Homo sapiens

<400> 263

```

cttccaactt ggtacctgtg gatatcatag aaagtgtagt ttcaaaggag atggacaaac 60
gatacttaca gtttgatatt aaggcctttg ttgaaaataa tcctgccatt aaatgggtgtc 120
ctactccagg ctgtgacaga gcagtaagac taacgaaaca aggggtcaa atacctggat 180
ctgatacact cagcttccca ttgctgagag ctctctgctgt tgattgtgga aaaggacacc 240
tcttctgctg ggagtgcctt ggtgaagcac atgagccttg tgactgccaa acatggaaga 300
attggctgca aaaaataacc gaaatgaaac cagaagaact tgtgggagtt agtgaagcct 360
acgaggatgc cgccaattgt ctctgggtat taactaactc caagccttgt gccaaactgta 420
agtctccaat acagaagaat gaaggctgca atcacatgca gtgtgctaag tgcaagtatg 480
acttttgctg gatttgcctt gaagagtgga aaaaacatag ttctgtccact ggagggttatt 540
acagatgtac tcgctatgaa gtcattcaac acgtggagga gcaatccaag gaaatgactg 600

```

167

```

tggaggctga gaaaaaacac aaacgatttc aggaacttga cagatttatg cactattata 660
caagatttaa aaaccatgag catagtattc agctagaaca acgccttctt aaaacagcca 720
aagaaaagat ggagcaattg agcagagctc tcaaagaaac tgaaggaggc tgtccagata 780
ccactttcat tgaagatgca gttcatgtgc tcttaaaaac tcggcgcatc ctcaagtgtt 840
cttatccata tggatttttc ttggaacctt aaagcacaaa gaaagaaatt tttgaactaa 900
tgcaaacaga cctagaaatg gtcactgaag accttgccca gaaagtcaat aggccttacc 960
ttcgcacacc ccgccacaag atcatcaaag cagcatgcct tgtacagcag aagaggcaag 1020
aattcctggg catctgtggg ctcgggggag tagctcctgc agactcacca gaagcttcca 1080
aggcgcatth tgstggtggg aacatggggr ttggggrata tttwggggtt tt 1132

```

<210> 264

<211> 499

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (447)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (466)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (467)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (469)

<223> n equals a,t,g, or c

<400> 264

```

ggcacgagtg aagctgaagt actgcttcac ctgcaagatg ttccggccac cccgaacctc 60
acactgcagt gtctgcgaca actgtgtgga acgatttgac catcactgcc cctgggtggg 120
caactgtgtg gggagacgga actatcgctt cttctacgcg tttattctct cctctcatt 180
cctgacggcc ttcactcttg cctgtgtggt caccacactg acgttgcgcg ctcagggaag 240
caacttcctc tccactctga aggagacacc agcaagcgtg ctgggagttg gtgatctgct 300
tcttctccat ctgggtccatt ctgggcctct cagggtttca cacgtacctc gtcgcctcca 360
acctgactac taatgaagac atcaaagggt cgttgggtcca gcaagagggc ggtgagcctc 420
ttgtcaaccc tacagcataa agtatnttca ccaatggcgg gtgggnntng ggccctaact 480
tccagctatt gacggggggg

```

<210> 265

<211> 735

<212> DNA

<213> Homo sapiens

168

<220>
 <221> misc feature
 <222> (648)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (713)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (730)
 <223> n equals a,t,g, or c

<400> 265
 ggagacacca ccattcctct cagcctgtgt ctgtctcaaa ggccccacct cacctcccct 60
 aaaggcagcc gctgcagtcg ccacaccttt gccctgtctg cgatgaccct gtcgccactt 120
 ctgctgttcc tgccaccgct gctgctgctg ctggacgtcc ccacggcggc ggtgcaggcg 180
 tcccctctgc aagcgttaga cttctttggg aatggggccac cagttaacta caagacaggc 240
 aatctatacc tgcgggggcc cctgaagaag tccaatgcac cgcttgtcaa tgtgaccctc 300
 tactatgaag cactgtgcgg tggctgccga gccttctga tccgggagct cttcccaaca 360
 tggctgttgg tcatggagat cctcaatgtc acgctgggtgc cctacggaaa cscacaggaa 420
 caaawtktca ktggcagggtg ggagttcaag tgccagcatg gagaagagga gtgcaaattc 480
 aacaagggtg aggccctgct gttggatgaa cttgacatgg agctagcctt cctgaccatt 540
 gtctgcatgg aagagtttga ggacatggag agaagtctgc cactatgctg cagctctacg 600
 cccaggctgt cgcagaacta tcatgagtgt gcaatgggac gcggcatnag tcatcacgca 660
 acgccacgac agatctctca gcacaaagat atgtcctggg acgcaatgga acntgagata 720
 accagtctan ctggtt 735

<210> 266
 <211> 851
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (834)
 <223> n equals a,t,g, or c

<400> 266
 ctattggtgt gaacagtgtg atgtacaatt ctctcaagc agtgaactct acctacattt 60
 ccaggagcac agctgtgatg aacagtactt gtgtcagttc tgtgaacatg aaactaatga 120
 tccagaagac ttgcatagcc atgtggtaaa tgagcatgca tgtaaattaa tagagtttaag 180
 tgataagtat aacaatgggtg aacatggaca gtatagcctc ttaagcaaaa ttacctttga 240
 caaatgtaaa aacttctttg tatgtcaagt atgtggtttt cggagtagac ttcacacaaa 300
 tgttaacagg catgttgcta ttgaacatac aaaaattttt cctcatgttt gtgatgactg 360
 tgggaaaggc ttttcaagta tgctagaata ttgcaagcat ttaaattcac atttatctga 420
 agggatttat ttatgtcaat attgtgaata ttcaacagga caaattgaag atcttaaaat 480
 tcatctagat ttcaagcatt cagctgactt gcctcataaa tgtagtgact gcttgatgag 540
 gtttggaagt gaaagggaaat taataagtca ccttcagtc catgagacaa cttgattatt 600

169

```

ctctttaact tacagaatgt tagtttaaaa taataaattc atcctttttt tggagatgat 660
taaattggatg attgttaaaca caacttatga aatctgcctt taacaagtaa ctttttttaa 720
ttataaaatt ttattggcat tgctccattt tctgtatata aatatacttt taatgtggta 780
ttttcaaaaa aaaaaaaaaa aaaaaaatcc acgcggccgc gaattcccgg gtcnaacaag 840
ctcactaatc c 851

```

```

<210> 267
<211> 1257
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (51)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (118)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1213)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1217)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1238)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1245)
<223> n equals a,t,g, or c

```

```

<400> 267
tcccgggtgtt tgggtggatgt ggtgggtcgcc aaagaagagt tagccattcc naccgcagat 60
tcaaattcga acaggccaaa gtttcagcct gtatattgcg cgcaatcatc agcgggaacncg 120
gtgatgaagt gatcgaaactg gcgaaaacaa atgggctaagg taaaaagggg ggcattttccg 180
tcataataag gacatgccat gattgattta cgcagtgata ccggttaccg accaagccgc 240
gccatgctcg aagcgatgat ggccgccccg gttggggacg acgtttacgg agacgaccct 300
accgttaatg ctctgcagga ctacgcagca gagctttccg gttaaagaagc cgccattttt 360
ctgcctaccg gcaactcaggc caacctggtc gctctgctca gtcactgcga acgcggcgaa 420
gagtatattg tcgggtcaggc cgcgcataac tatctgtttg aagccgggtg cgcgggcggtg 480
ctgggcagta ttcaaccgca acccatagac gcggctgccg acggcacgct accgctggat 540

```

170

aaagtggcga tgaaaatcaa acccgacgat atccatttcg cccgcaccaa attactcagt 600
ctggaaaaca cccacaacgg caaagtgttg ccgcgggaat acctgaaaga agcatgggaa 660
tttaccgcg agcgcaatct ggcgctgcat gttgacgggtg cgcgcatctt taatgccgtg 720
gtggccttacg gctgcgaact gaaagagatc acgcaatatt gtgattcgtt caccatttgc 780
ctgtcgaaaag gtcttgggac gccagtcggt tcattactcg tcggtaatcg tgattacatt 840
aaacgtgccca ttcgctggcg gaaaatgaca ggtggcggga tgcgccagtc cggcattctg 900
gctgccgcgc ggatatatgc cctgaaaaat aacgttgccg gcttgccagga agaccacgac 960
aacgctgcct ggatggcggga cagctgcgtg aarcargcgc ggatgtgatg cgtcaggaca 1020
ccaatatgct gtttgttcgc gtcggggaag aaaatgctgc cgcgtaggc gaatacatga 1080
aagcgagaaa cgtgctgatt aacgcctcgc cgattgtccg cctgggtgacg catcttgacg 1140
tctcgcgcga acaactggcg gaagtcgccg cccactggcg tgcattcctg gcgcgttaag 1200
gagagaaacg ttncgcnaag cattttagtt ctccgtgnca attgntacat tgtcaac 1257

<210> 268

<211> 1085

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1067)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1081)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1083)

<223> n equals a,t,g, or c

<400> 268

gcaaaatttt agcatctctc aataatcata ctttttctct ttaattatca acaaaatatt 60
ttcatgttaa gctatctctt gcatccttag aataactcta cttgatcatg atgttttttc 120
ttttaataat ggaattataa ataagtatac agtttttgta tgaaaatgtt tttattttctc 180
tggagcatgt acctatggat ggaattacta aatcatatgc tagttctgtg tttaactatt 240
tgaaggattg aaggagtgcc agattgtttt ccaaagtggc tgtaccattt tacattccta 300
cctgcagtgt atgaaggttt caatttctcc acatcctcac caatattatt atctgtcttt 360
ctgattgtag ccatcctagt ggggtgtgaag tggatatctt gtgacttgga tttgattttc 420
cctgatggct aatgatattg aacatctatc tttctctgtg cttattggtc atttgtatat 480
tttcttttga gaaatgtcta ttccagatcc yttttctgtt tttaaaaaat arctttattg 540
aggtwtatth gacaaataaa aatttgktgt atatttataa tgtatttata agaaaattga 600
gagaaaggac tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattata 660
atgaagggtga cttaaacagc ttaaagttta gtttaaaagt ttaggtgat taaaataatt 720
tgaaggcgat cttttaaaaa gagattaaac cgaagggtgat taaaagacct tgaaatccat 780
gacgcaggga gaattgcgtc atttaaaagc tagttaacgc atttactaaa cgcagacgaa 840
aatggaaaaga ttaattggga gtggtaggat gaaacaattt ggagaagata gaagtttgaa 900
gtggaaaact ggaagacaga agtacgggaa ggcgaagaaa agaatagaga agatagggaa 960
attagaagat aaaaacatac ttttagaaga aaaaagataa atttaaacct gaaaagtagg 1020

171

aagcaraara aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgcncctg gggccccagc 1080
ntncg 1085

<210> 269
<211> 1315
<212> DNA
<213> Homo sapiens

<400> 269
ggcggcagcg ccggaaagga ggccaagagc gcggggcggcg aggcaagatg gcggcaacca 60
agaggaaacg gcgtggaggc tttgcagttc aggcgaagaa gccaaaaaga aacgaaatag 120
atgcggagcc gccagctaag cggcacgcca cagcagagga ggtggaggaa gaagagaggg 180
accggatccc agggcccgtt tgcaaggga agtggaaaaa taaggacgg attctcatct 240
tttcttccag aggaataaat tttagaacaa gacatttaaat gcaggacttg agaatgttga 300
tgcctcattc taaagcagat actaaaatgg atcgtaaagga taagctattt gtgattaacg 360
aggtttgtga aatgaagaac tgtaataaat gcatctattt tgaagctaag aaaaaacagg 420
atctctatat gtggctttca aattcacctc acggaccatc tgctaaattc cttgttcaaa 480
atattcatac cctcgttgaa ctgaagatga ctggaaactg tttgaaagg tctcggcccc 540
ttttgtcttt tgaccctgct tttgatgaat taccacatta tgctttgkta aaagaactct 600
taattcagat ctttagtaca ccacggtatc atcccaaaag ccaaccattt gtggaccacg 660
tgtttacttt caccatthttg gataatagga tatggtttcg gaactttcag atcatagaag 720
aagatgctgc tctttagtaa ataggacctc gttttgtctt aaatctcata aagatthttc 780
agggaagttt tggaggacca actttatatg aaaatcctca ctaccagtca ccaaactgc 840
atcggcgtgt cataagatcc atcacagctg caaaatacag agagaaacag caagtgaag 900
atgtgcaaaa actgagaaag aaagagccga agactcttct tccacatgat cccactgcag 960
atgtttttgt aacaccagct gaggagaaac caatagaaat acagtgggta aaaccagagc 1020
caaaagttga tttgaaagca agaaagaaac ggatttacaa aaggcaaaga aaatgaaac 1080
agaggatgga cagtgggaaa acaaaataag tcaatggaaa cctgatttgt ttttcagtta 1140
ctttatattht atthttgtatt caatgtgtaa atactthtat tatctaatac tatcttacgt 1200
ctaattagtg tagcatttac aagaaagaaa aattaagatc ttaaaatcag tgattatctt 1260
tttctaaata aaatatcacc agaattcatc agttaaaaaa aaaaaaaaaa aaaaa 1315

<210> 270
<211> 2959
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2948)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2956)
<223> n equals a,t,g, or c

<400> 270
ccattccccg gtcgacccac gcgtccgctg gaaatttgga ttctccagaa ggtggtttcg 60
atgccatcat gcaagttgca gtttgtggat cactgattgg ctggaggaaat gttacacggc 120
tgctggtgtt ttccacagat gccgggtttc actttgctgg agatgggaaa cttggtggca 180

172

```

ttgttttacc aaatgatgga caatgtcacc tggaaaataa tatgtacaca atgagccatt 240
attatgatta tccttctatt gctcaccttg tccagaaact gagtgaaaat aatattcaga 300
caatttttgc agttactgaa gaatttcagc ctgtttacaa ggagctgaaa aacttgatcc 360
ctaagtcagc agtaggaaca ttatctgcma attctagcaa tgtaattcag ttgatcattg 420
atgcatacaa ttccctttcc tcagaagtca ttttggaana cggcaaattg tcagaaggmg 480
taacaataag ttacaaatct tactgcaaga acgggggtgaa tggaaacaggg gaaaatggaa 540
gaaaatgttc caatatttcc attggagatg aggttcaatt tgaaattagc ataacttcaa 600
ataagtgtcc aaaaaaggat tctgacagct ttaaaattag gcctctgggc tttacggagg 660
aagtagaggt tattcttcag tacatctgtg aatgtgaatg ccaaagcgaa ggcatccctg 720
aaagtcccaa gtgtcatgaa ggaaatggga catttgagtg tggcgctgac aggtgcaatg 780
aagggcggtg tggtagacat tgtgaatgca gcacagatga agttaacagt gaagacatgg 840
atgcttactg caggaaagaa aacagttcag aaatctgcag taacaatgga gagtgctct 900
gcgacagtg tgtttgtagg aagagggata atacaaatga aatttattct ggcaaattct 960
gcgagtgtga taatttcaac tgtgatagat ccaatggctt aatttgtgga ggaaatgggtg 1020
tttgcaagtg tcgtgtgtgt gagtgcaacc ccaactacac tggcagtgca tgtgactgtt 1080
ctttggatac tagtacttgt gaagccagca acggacagat ctgcaatggc cggggcatct 1140
gcgagtgtgg tgtctgtaag tgtacagatc cgaagtttca agggcaaacg tgtgagatgt 1200
gtcagacctg ccttggtgtc tgtgctgagc ataaagaatg tgttcagtgc agagccttca 1260
ataaaggaga aaagaaagac acatgcacac aggaatgttc ctattttaac attaccaagg 1320
tagaaagtcg ggacaaatta cccagccgg tccaacctga tcctgtgtcc cattgtaagg 1380
agaaggatgt tgacgactgt tggttctatt ttacgtattc agtgaatggg aacaacgagg 1440
tcattggttca tgttgtggag aatccagagt gtcccactgg tccagacatc attccaattg 1500
tagctgggtg ggttgcctga attgttctta ttggccttgc attactgctg atatggaagc 1560
ttttaatgat aattcatgac agaagggagt ttgctaaatt tgaaaaggag aaaatgaatg 1620
ccaaatggga caggggtgaa aatcctattt ataagagtgc cgtacaact gtggtcaatc 1680
cgaagtatga gggaaaatga gtactgccc tgcaaactcc acaacactga atgcaaagta 1740
gcaatttcca tagtcacagt taggtagctt tagggcaata ttgcatggg tttactcatg 1800
tgcagggttt gaaaatgtac aatatgtata atttttaaaa tgttttatta ttttgaaaat 1860
aatgttgtaa ttcatgccag ggactgacaa aagacttgag acaggatggg tattcttgtc 1920
agctaagggt acattgtgcc tttttgacct tttcttctct gactattgaa atcaagctta 1980
ttggattaag tgatatttct atagcgattg aaagggcaat agttaaagta atgagcatga 2040
tgagagtttc tgttaatcat gtattaaaac tgatttttag ctttacaat atgtcagttt 2100
gcagttatgc agaatccaaa gtaaatgtcc tgctagctag ttaaggattg ttttaaactc 2160
gttattttgc tatttgctct ttagacatga ctgatgacat atctgaaaga caagtatgtt 2220
gagagttgct ggtgtaaaat acgtttgaaa tagttgatct acaaaggcca tgggaaaaat 2280
tcagagagtt aggaaggaaa aaccaatagc tttaaaacct gtgtgccatt ttaagagtta 2340
cttaatgttt ggtaactttt atgccttcac tttacaaatt caagccttag ataaaagaac 2400
cgagcaattt tctgctaaaa agtccttgat ttagcactat ttacatacag gccatacttt 2460
acaaagtatt tgctgaatgg ggaccttttg agttgaattt attttattat ttttattttg 2520
tttaatgtct ggtgctttct atcacctctt ctaatctttt aatgtatttg tttgcaattt 2580
tggggtaaga ctttttttat gagtactttt tctttgaagt tttagcggtc aatttgcctt 2640
tttaatgaac atgtgaagtt atactgtggc tatgcaacag ctctcaccta cgcgagtctt 2700
actttgagtt agtgccataa cagaccactg tatgtttact tctcaccatt tgagttgccc 2760
atcttgtttc acactagtca cattcttgtt ttaagtgcct ttagttttta cagttcactt 2820
tttacagtgc tatttactga agttatttat taaatatgcc taaaatactt aaatcggatg 2880
tcttgactct gatgtatttt awcaggttgt gtgcatgaaa tttttataga taaagragtt 2940
gaggaaanaa aaaaanaaa 2959

```

<210> 271

<211> 2025

<212> DNA

173

<213> Homo sapiens

<220>

<221> misc feature

<222> (1339)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1916)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1944)

<223> n equals a,t,g, or c

<400> 271

```
ttatttttaca gcttcaaata tttctcatta tcttgctact tagttcttca tgtttctcct 60
tctgactttt aataatggta ataggaaaac aaaacccaaa gcttttcaga acttcagtgt 120
gaggtttctt attttracaa gttaacttgt aaatactcag gttttacgat gtataattta 180
cctaatagac caaactaact catggagata ttttgaacta ttatttaggt acaaacttta 240
taaagaatgt tagtatgtca taaaatataa cattacagct tatttaaaac caaatatagt 300
tgaacatatt taaaatacat tttcacagaa tggatgaatt agttgtttct tcagagttac 360
ttatgaacag ttgaatgctt taaaatgttc tgtctgtagg taacatctaa aacacaagtg 420
ggttttattta aattttttaa atttgaaatt ttttatttgc aaaaaattgt tttatgcttt 480
attatatcgc aaatgagtggt cagatttttg agtaccaatg atcatgcttc catttttttt 540
agtttttaaac caccaaacca atatttttcc tttaaatttt aatcttataa tatagaaatc 600
ttatgtaaat gaaattttgt catgtttcaa ataaagagaa ctgaagtaga aaatagaaat 660
gccagtaaac aacataatgt ttaattttaca acttacatta ggggtttggg ggaatgctaa 720
ttatatattg agaataataca ttagaactct tcaaaatggg ctcttctaat gaggtcacta 780
ctgaacaaaa ttgttccctc ttctgttaaa tagaatagggt ttaaatgact agtcaaatga 840
attattttct tcttgtaaaa taaattaaat cttactttct tttaatgacc aaccttaggt 900
aaaacaaaaa tattgtaatc ctagaaatta tcctccagct ttctcacctg aaaatctatt 960
gaagtgatcc ctgggtcatcc taataatggg atgagggaag tttccagcag atttcagggt 1020
gttcttaaaag tttttgttgg tcattttctc aatagtagat gaaatcaaga tgcttatgag 1080
catggaaatg tatttaaaagt ttttgcttgt gtccctctca gtcagaatag aaaagtaact 1140
gaaatactct tacctttctg tccttgataa aatagtaaaag aaaaccaaac aaaccaggc 1200
ctgatgggaa aaatgattcc tttattctag caacttactt tctgttggtg tgggaaatgt 1260
tattaatttc tattactaaa gttcatatca caaaatgata ttttaataa accttgggggt 1320
aaatcatgaa ttttttttnc tacgtgtgag tataaaagac aaaagttgaa cagcatggaa 1380
tctcattgcc aaattattag tgaatgtata gttcagggtat tctttgagac acacagtatc 1440
attaatttcc gaattgtatt tcagtgttat tttttgtttg tgaccactaa gcttctgtct 1500
taatacaaaag ctgttacctt ctacagaatt taagtctgaa gatgtaaaga gagaacaggc 1560
cttgtgtaac agaagatact cttttttatg ctcccttactg tgatcacaga aaaattaaaa 1620
atccaagtgc tctctagatt tgttgataaa cattttatgc ttgcatttaa acttgaaatg 1680
tatgagcaga atgagacaat cagttaaatc agaaatgaga agtattataa tgtaaaggcc 1740
ttgttttgct gtagcaataa aatgaccaag tgcaatgact tgatttaata aaatcatatt 1800
ttaaaagtgc tgstatgaaw atttttggct ataaaaatttt accctgactt gstttcaata 1860
actgttacgt aatgcagttt gatgttgtaa cctaacattc caaaaaaaaa attganaggg 1920
ggaatctcaa aatagtatat actncaactaa cttgttttaca ggtgctgtat ttaaaagcat 1980
```

174

gctttctctct caaaaagaaa aattaaagga ttttattgcc aaacc

2025

<210> 272

<211> 852

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (767)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (769)

<223> n equals a,t,g, or c

<400> 272

```
ccaccgcgcca caaggcccag ctaatTTTTg tatttttagt agagacaggg tttgattatg 60
ttggacagggc tgggtctcaaa ctcttgactt caagtgatcc acccgctctg gcctcccaac 120
gtgawggggac tatagacatg agccatcgtg cytggccttc ttgawtcttg aatacggggg 180
tttgagggtga aagcattttca tgaaaactta agttcataca caagagcatc atgaatattc 240
taaaagagggt atctgtgctt tttttgtgac cacaaaatat tacttcttat gaaatgttta 300
cactagggtga ggaaaagtgc attaattacc tttaaaccgt tccttatttt ttttaagatt 360
ttaaattgta ttttggtctt tgccctccagt atcccttctg gttgctctgg tttgaattaa 420
gttcctatta tgctgcagca catatcaacc ttccctaagt aaccatttcc tggaatgtga 480
agcatcggtg ccattagcag accatatgca gaaatgtcgt gtacttgcac ttcttttttg 540
tgcactctat aaggctgggt gtgactcaga tcagcttaac tttttatatt atgttatttc 600
actaactgct acagtcaaaa tgatcaaata tttgtacaat agaaaattat tttaatttta 660
tttttctact gacattttcta attctagtgt aaatgtttat caataaaaaa ttactttcaa 720
ttctgagttg gaattatatt tctttttggg ggctaaatga ggttaancnt ttggaataaa 780
aatgacttcc aagttttcaa ttttttaaaa taacttaaaa atcttagcaa ggggggaaact 840
tttttttaag gg 852
```

<210> 273

<211> 571

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (535)

<223> n equals a,t,g, or c

<400> 273

gcccantac tttccagccc agtaaggggt atttcaggag agcagtccac tkaaggttct 60

175

```

ttccctttaa gatatgtgca ggatcaagtt gcggcacctt ttcagctgag taaccacact 120
ggccgcatca aggtggtcct tactccgagc atctgtaaag tgacctgcac caagggcagc 180
tgtcagaaca gctgtgagaa ggggaacacc accactctca ttagtgagaa tggtcâtgct 240
gccgacaccc tgacggccac gaacttccga gtggtaatth gccatcttcc atgtatgaat 300
ggtggccagt gcagttcaag ggacaaatgt cagtgccttc caaatthcac aggaaaactt 360
tgtcagatcc cagtccatgg tgccagcgtg cstaaactth atcagcattc ccagcagcca 420
ggcaaggcat tggggacgca tgtcatccat tcaacacata ccttgctctt gaccgtgact 480
agccagcagg agtcaaagtg aaatttcttc cttaacatag tcaatatcca tgtgnaacat 540
cctcctgaag ctccggtcca gatacatcag g                                     571

```

<210> 274

<211> 710

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (667)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (689)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (701)

<223> n equals a,t,g, or c

<400> 274

```

gtaagtttga gagcatctgc tggaaaacca ctagaatttg caaacggcca cctcaaaata 60
ctccagccag tcccactaag ccaaagacca gaatctgaga acagggatgg ggaaattatt 120
cctttctgtg gatgattatg cagctggggc atgatttcac acccgggggc catgggctaa 180
gatggagggg aaggaaggaa tgtaatgtgt gccctctacc tcttcaccag gcatcatcct 240
ctcactggcc ctggctggca ttcttggcat ctgtattgtg gtggtggtgt ccatttggct 300
tttcagaagg aagagtatca aaaaagggtga taacaaggga gtcatttaca agccagccac 360
caagatggag actgaggccc acgcttgagg tccccggagc tccccgggca catccaggaa 420
ggaccttgct ttgggacctt acacacttcg gctctctgga cacttgcgac acytcaagggt 480
gttctctgta gctcaatctg caaacatgcc aggcctcagg gatcctctgc tgggtgcctc 540
cttgcttgg ggacctggc caaccagag ccatecgatt cgatggatgg ggatgcactc 600
ttcagaccaa gccagcagga attccaaagc tgcttgctgt aaatgtgtga gattgtgaat 660
gggctgnatt ctggattcaa aaccagccng ctgggtgggc ntaaggttgg                                     710

```

<210> 275

<211> 595

<212> DNA

<213> Homo sapiens

<400> 275

```

taaaagagtg tcctaacagt cccccgggcta gagaggacta aggaaaacag agagagtgtt 60

```

176

```

acgcaggagc aagcctttca tttccttggt gggggagggg ggcggttgcc tggagagggc 120
cggggtcggg gaggttgggg ggtgtcagcc aaaacgtgga ggtgtccctc tgcacgcagc 180
cctcgcccg cgtggcgctg acactgtatt cttatgttgt ttgaaaatgc tatttatatt 240
gtaaagaagc gggcggtgac cctgctgcc cttgtccctt gggggtcaca cccatccctt 300
ggtgggctcc tgggcggcct gcgcagatgg gccacagaag ggcaggccgg agctgcacac 360
tctccccacg aaggtatctc tgtgtcttac tctgtgcaaa gacgcggcaa aaccacgtgc 420
cctgggtttt cccacccga gatgaaggat acgctgtatt ttttgccctaa tgtccctgcc 480
tctaggttca taatgaatta aaggttcatt aacgctgcga aaaaaaaaaa aaaaaaaatt 540
tgccctatca gtgagtcgga ttaattgtcc gcgcggccgg acatttagta gtagt 595

```

<210> 276

<211> 1172

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (119)

<223> n equals a,t,g, or c

<400> 276

```

tactatttat agcttttagat agggcctccc ttcccctctt ctttctttgt tctctttcat 60
taaaccctt cccagtttt ttttttact ttaaaccctg ctctcatgg ccttggcctt 120
ttctgaagct gcttctctt ataaaatagc ttttgccgaa acatagtttt tttttagcag 180
atcccaaat ataataaggg ggatgggtgg atatttgtgt ctgtgttctt ataatatatt 240
attattcttc cttggttcta gaaaaataga taaatatatt tttttcagga aatagtgtgg 300
tgtttccagt ttgatgttgc tgggtggttg agtgagtga ttttcatgtg gctgggtggg 360
tttttgctt tttctcttgc cctgttctct gtgccttctg atggggctgg aatagttagg 420
gtggatggt ctacccttct tgccttctgt ttgggaccca gctgggtgtt tttgggttgc 480
tttcttcagg ctctagggct gtgctatcca atacagtaac cacatgcggc tgtttaaagt 540
taagccaatt aaaatcacat aagattaaaa attccttctt cagttgcaat aaccacgttt 600
ctagaggcgt cactgtatgt agttcatggc tactgtactg acagcgagag catgtccatc 660
tggtggacag cactattcta gagaactaaa ctggcttaac gagtcacagc ctcaagctgtg 720
ctgggacgac ccttgtctcc ctgggtagga ggggggggaa tgggggaggg ctgatgaggc 780
cccagctggg gcctgttgtc tgggaccttc cctctctctg gaggggaggg ctggtggctt 840
agcctgggca ggtcgtgtct cctcctgacc ccagtggctg cgggtgagggg aaccaccttc 900
ccttgcctga ccagtggcca ttagctcccg tcaccactgc aaccagggt cccagctggc 960
tgggtcctct tctgccccca gtgcccttcc ccttgggctg tgttggagtg agcacctctt 1020
ctgtaggcac ctctcacact gttgtctgtt actgattttt tttgataaaa agataataaa 1080
acctggtact ttctaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140
aaaaagggcg gccgtcgcg atctagaact ag 1172

```

<210> 277

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (161)

<223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (773)
 <223> n equals a,t,g, or c

<400> 277
 cgcggaacaag gccaggctag ccttgagctc cgtcgggcag ggcgccggga ttggtgtccg 60
 gcagagcgtg agccagcggg gcgamgtcgg cgagcgggag tgaaagaaga aaagctagag 120
 agcgaaggca aagccgagga gagagggccg cggtcggcga nggaatctga ctgcacgggt 180
 gcgtgcgctc acttccggag gctccctcag scgggcggct ccgstagtgg ctaaaggcaa 240
 agcattccgg ggcgcgggcg atgaagttga gcttcgtccc tgctagccgc cgctttctcc 300
 ccaaaaatac atcctagcct taatgtttat gcctccattg cccagttct tatctgtttt 360
 gctcaatgtc tcatagctac aagaaggcaa tttctgacga agccctccgt sccttccaaa 420
 tggattattht tggcgggctt ycaccgggac agtatgccac ccgaatgact ggacaagtgc 480
 acgggagcgg ctgtcatttg cggagtgcgc cttgcgatct aggcgcctca cagcgmaayt 540
 atccagtaat ttctctgaaa tcgatgctgg tttgttttcc caaggcaaat cagcagctta 600
 tacagacatt ggggccacaa agccggtgga acaacgggag acggcttctt gagtgtcagg 660
 tcctccaaga tgagcttaaa mttcgggtgg tgggcaggyt cgtaggcggg aaaggscctg 720
 gtccagatgr atgcaktcca tgtatatatt gatgaaagac acgtatacca ttnggtcaag 780

<210> 278
 <211> 2375
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (9)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (920)
 <223> n equals a,t,g, or c

<400> 278
 cggcagcgna ccaagatggc ggcgccctgt gagggacaag cgtttgccgt agggttgaaa 60
 agaattgggg tgcagtagtt cgctccccag aagggaaccc ccagaaaatc cggcagctga 120
 tagatgaggg gattgccccg gaagagggag gcgtggacgc gaaggacacg tctgccacat 180
 cccagtcagt taatggatca cccaagcgg aacaaccttc attggaatct acaagcaaag 240
 aagccttctt tagcagagtg gaaacatttt cttctttgaa atgggcagggt aagccctttg 300
 agctgtctcc actcgtctgt gcaaaatatg gctgggtcac agtggaatgt gatatgctca 360
 agtgctctag ctgtcaagct tttctctgtg ccagtttaca accagctttt gactttgaca 420
 gatataagca acgatgtgct gagctgaaga aagccttgtg tactgcccac gagaagttct 480
 gtttctggcc agacagccca tccccagacc gatttgggat gttgcccctg gatgagcctg 540
 ctattcttgt tagtgaattc ctagatcgtt ttcaaagcct ttgtcacttg gacctccagc 600
 ttcttccctt aaggccggag gacttgaaaa ctatgtgctt gacagaagac aagatcagtc 660
 ttctcctaca cttgcttgaa gatgaacttg atcacgaac tgatgagaga aaaactacaa 720
 tcaaattagg ctcagacatc caagtccacg tcaactgctg tattctctct gtgtgtggct 780
 gggcgtgtag ttctcttttg gaatccatgc agctctccct gatarcatgt tcgcaatgta 840

178

```

tgargaargt ggggctcttg ggcttccagc agattgaatc gtccatgact gacctggatg 900
catcttttgc tgaccagctn cccaatccca ggccttgagg ggcgaccaga gcgcttacct 960
ctggtgcctg aatctcctcg gaggatgatg acccgagacc aggatgccac tttctcccca 1020
ggctcagagc aggctgaaaa gagccctggg cccattgtct cwcgaactcg gagctgggac 1080
tcttccagtc ctgttgaccg tcttgagcca gagctgctag ccccaccacc agaactcgcc 1140
cagtgaccgg aagcatggga acaggagaca cccctggcct ggaggtacca tctagccctc 1200
tgcggaaagc aagcragctc gcctctgctc ctccagcagt tcggacacat cttcccgaag 1260
cttctttgat cccacctctc agcatagaga ctggtgcccct tgggtgaata tcacacttgg 1320
caaagaaagc agggagaatg gtggaactga accagatgcc agcgccccag cagagccagg 1380
ctggaaagca gtgctgacca tctctttggc gcacaaacag tctagccagc cagctgaaac 1440
ggactccatg agtctctctg agaaatcaag gaaagtattc cgaatatttc ggcagtggga 1500
atctctgtgc tcatgtgaa gatactccag cgccttcctg gagatagctg gaatgagagt 1560
gactttttga aaaattaagg ctgagttcct ttccggtcagc tgacactaag ttttccctgt 1620
tctgggttaa tcataaggag cccctgcca tagcaaaggc agtgagtgtc aactatctgc 1680
atctggctga gagagaccgg tttcctttca gggatgtgga cagggttaagg gcagcaagca 1740
tggttctgtt aaaggagtgt ggggttaaca gactagaagg aagactaagg acctgaccac 1800
ccatttcagc atcttcaatg tggagcagtg ttctgaggac tcttctatcc taggactatg 1860
acagtgtgta ttaataaaat atttgctaag attctcattg ttggagaact gttttccccc 1920
ttgccctgtg ggccggagaa acttcagtgg aacattcaac ttttgatttt cagattggct 1980
gcaaagcctw aaatttgkga ttccagtcaa ggaggtataa tctttcctwa accaaaagca 2040
agatgatttt cattatgcca ccaggaaatt tcttggtgtg ttatagttaa tgggtcaactg 2100
ataattttct ccttgctttg ataataacag aataaaacaa cgtaatgggg aggaaggcac 2160
ttcagaagar acccctytcc atgtgccatt gaatgcatga gtcccccart tgggcttccc 2220
caagactcgt tgctttttggg ggatcatcag tttttgtggg agagaagggtg gacctgaac 2280
tgcccaactga taaagtaacc atgacctagc aaaggctaga aagtgattat tctctgatat 2340
ggccatgttt ttcgtcactg agattgtttc tcgtg 2375

```

<210> 279

<211> 2461

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1164)

<223> n equals a,t,g, or c

<400> 279

```

tttcaattct tggntttctg ttcccttcta ccaaaaccca gcataggact cagtgtacac 60
ttacttttaa aaaaaaactc acattttcta gctgcagggt atggcctcag tcattttaaat 120
acagccttga atgagtttgc ttattaccca gtcactttcg tagtgaatgt tcaaacccca 180
aagcaaatgt ttgcatctcc ttgtccataa aggagaaagc cagggttatag gagaaagaga 240
gagaaaggcg catgtctgtt tgcacagaga gaggcaattt tgtctacctt tcgagaatca 300
gttataaaca gaagggcctc ttaggatttt gagctctcct gacaatgaag gaaaagctct 360
cttgagtata caagttccac actcattacc tttcagtggt gacccatcac cactacaat 420
ttgttgaagg aagggtgtgt cagagatatg ctttaaagtt gtacttttagg ctgaaattct 480

```


179

```

ctctgtatatt ggacctgcag atgttgtgta cagaaccgat gcatggcagg gtcaggaagc 540
taggagagtg aaggcgcttg tggagacagc tctgtagcaa atgaaacacg gaagcctccg 600
ggaatgtggt tgtgtcacca gcagcaggca tttccctgtc cteccacccc ccagtctcca 660
catccccagc agcctcttcc agaagcatgt cagggagacg gacagggtgt ctccttctcg 720
tgcaccacat ccaagtccac ccaccgtgga cgcagtgtga ctaaagtctg gccttgaaga 780
gaaaccctca gccagcttgt ctgltgtcca ggtccctcag tgtctctggt ttccctgccc 840
tgcataattt aagcattagt gccaaataca tctgtcatal tctctctccc ggagactgcg 900
aaatgtccag actttttcag actagtggag ggaaggaatg ttacataact aagtggaggc 960
ctggaactgt caggatttga cagggtcaga ccagagaccc ttccgcctct gcctagtgtg 1020
tctgtcaggc aggcagcagc catcaatcca agaagagacc atggcgcaa gcactktgtg 1080
gagaaaggaa cccagccgag gtctgagttt cagacagaaa ctggggagtt gggacatctt 1140
ctctgtgcca ggcttcattg acancatcgg tcttcattg asctgagccc aagccctcag 1200
tggaacctgt caagagcatc agcagcatgg agctgaagac cgagcccttt gatgacttcc 1260
tgttcccagc atcatccagg cccagtggct ctgagacagc ccgctccgtg ccagacatgg 1320
acctatctgg gtccctctat gcagcagact gggagcctct gcacagtggc tccctgggga 1380
tggggcccat ggcacagagc tggagccctt gtgactccg gtggtcacct gtactcccag 1440
ctgcaactgt tacacgtctt ccttcgtctt cactacccc gaggtgact ccttccccag 1500
ctgtgcagct gccaccgca agggcagcag cagcaatgag ccttccctct actcgctcag 1560
ctcaccacag ctgctggccc tgtgaggggg caggaagggg gaggcagccg gcaccacaa 1620
gtgccactgc ccgagctggg gcattacaga gaggagaaac acatcttccc tagagggttc 1680
ctgtagacct agggaggacc ttatctgtgc gtgaaacaca ccaggctgtg ggcctcaagg 1740
acttgaaagc atccatgtgt ggactcaagt ccttacctct tccggagatg tagcaaaacg 1800
catggagtgt gtattgttcc cagtgcactc tcagagagct ggtagttagt agcatgttga 1860
gccaggcctg ggtctgtgtc tcttttctct ttctccttag tcttctcata gcattaacta 1920
atctattggg ttcatatttg gaattaacct ggtgctggat attttcaa atgtatctagt 1980
gcagctgatt ttaacaataa ctactgtgtt cctggcaata gtgtgttctg attagaaatg 2040
accaatatta tactaagaaa agatacgact ttattttctg gtagatagaa ataaatagct 2100
atatccatgt actgtagttt ttcttcaaca tcaatgttca ttgtaatgtt actgatcatg 2160
cattgttgag gtggtctgaa tgttctgaca ttaacagttt tccatgaaaa cgttttattg 2220
tgtttttaat ttatttatta agatggattc tcagatatatt atatttttat tttatttttt 2280
tctaccttga ggtcttttga catgtggaaa gtgaatttga atgaaaaatt taagcattgt 2340
ttgcttattg ttccaagaca ttgtcaataa aagcatttaa gttgaatgcg aaaaaaaaaa 2400
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaagggcgggc cgctcgcgat ctagaactag 2460
t 2461

```

<210> 280

<211> 2520

<212> DNA

<213> Homo sapiens

<400> 280

```

accacttgca ctccagcctt gaacagagtt aggatcctgt caaaaaagaa aagaaaaaga 60
aagcagcatt caaatgtaag acaactgtaa aatattgagc cccacttggg ctaaaattca 120
aaaaagaaga cgcctgtcca tcgccttttt ataagtcctt ctctccacac ctaaaagcag 180
ctgcagctgg aagggcacia attccactgt gtaaaataaa atattagggg caacacactt 240
catcaaggca gcaggaatga gagagagcag agaagatcaa ggatgaagtc ttgggtactg 300
aaaaattcag tgctggggcag aaaaactgac agggcagtac aagtaacaaa cagaatccaa 360
gtgggggtgg ccttgtgcac agagctccag gtgacctctg gagagacatg ggcattcaca 420
tggaagctta aaacggaaag tcaagtttca tactcaacat aatcttctgt gtgacaaaag 480
acaagccatg tagcctctct gtgcctatct cttcatgcat aaactgggac tcataatatt 540
tgtaaaatgt attgatactc tcagggcaaa ttactatat tgctatacag ttgagatcag 600

```

180

```
tgttgtaaaa ttaaactgat ctgggttctaa ttgcctcaaa ggccaaagcc caggcatttg 660
aatggaaaag aagcagagag gaggctgact tagctgattg gtatggaaac agttggggcca 720
agagccagaa tttccctttg tagcaacacg gctagtttta ctttgagaag ctctgctcag 780
ctgctttata acattaagtc tggcggaatg gatgtcactg tgcacaataa agttttcaca 840
agtataaaca atggtgatgt aagtcaacat tgctgtagcc aggtgtgaag gttgtatggt 900
gtgtgacgaa tgtacatcat gtttgtaggt ttggatgcta atcttgaatt gtagyttaaa 960
aaatacgtat ttttgtaact ctttgaaagt ttatgaagac tgacagcttt ctttgaagc 1020
actaagagaa aaaaaagaaa gagggacatt tgacaatttt aaagaaacaa caagaaatta 1080
gaatgaaaat ctgtgacaaa cagcgtcagt gtggccatgt ccacattcct acatgtctct 1140
ctctacaagc acctctctaa gaagcctgac atcccggtgg actctttata gtcattgtaca 1200
cttgattcca gatgagctct ggtcttatct ggatgctcag ataagagggt tctatctgag 1260
catccaatgt tccctcaggt tccaagacat ttcacccag gccctgggtt tctctctggg 1320
aatctgtagg cttcacgtct ctctagaaat gacgtgtaaa atttaagacc agacctcagc 1380
catcagcgtc cagaccatcc tagaagtctt tcccaatctc acagagaaaag ccctagtatt 1440
tcccagtgac cccaggattc cacgttgggg tggccaaaga aatagggtctc tcagggcttt 1500
gccacagcct ccagcccatc cttcagaggc acacacagca cctctcggtt gctccagctc 1560
tgtaggatag cctccctctgg ggtccgtggg acgcggggcca cagtgttgag gtagacaagg 1620
aggatcagtg agaggcctct tccctctcca cagagactgg attgtcattg ttccttcatt 1680
tatatcgtag ggcttaacat ttcactcaaa aaaaagcccc tctttttcta atccttagtc 1740
tttgtttcaa ggaaagccag tttttcttct accacatttt ccaggatcga ctttaagaaa 1800
aatgcaacat ctattgaaaa aaagtggggt gtatgcatgt ggtttaattc cagattgctt 1860
ttgggtttta gtggtatcaa atttcagtat atttctgtct tatgtgaaag aaatatatta 1920
ctaaaacgtc agtgagcaat aatgtcagct gtcaagcact agatttattt ttgcaggata 1980
tggagtgcaa tgaactgagt caatatggca aggtgtatgt gatctgtggg agttatgcca 2040
tttaacatag gaagtgcatt ggactttccc tctctgcaat ccagctctta ctgtaccatt 2100
agaagatgca gaattctgtt ggtgtgcaaa aagtatagcc ttacattcaa gcagaatgga 2160
tctgaagaaa gcagcaatat ctgttactag agaacattcc catgtgttta aactcttcac 2220
ttcttagatg catttaaaatt cttaatgcaa atgacgtagc aatttgaaaa cttctccgta 2280
ttacttgtgt ttaaaatgtc ttgctttaaa taaaaacaa atggtaaagg ggattatctt 2340
ttgttttagat ggtaaataat tatttttgcc ttagatagct ttgtaataat ttttctccag 2400
acagttcaac acttttgaaa aatgacatga attttcatta aaaacccttt tcttatgttt 2460
attgtataca agaattatgc aataaaattt ctttataaaa ataaaaaaaa aaaaaaaaaa 2520
```

<210> 281

<211> 1448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1427)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1432)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1440)

181

<223> n equals a,t,g, or c

<400> 281

```

cagcgccact agcctcattg tgcccaggag ttctccaaac ccgcgctgcg gagtgagtga 60
ccaagttccg gccagttcga cctcgaggat ccagaggtgg agacggtact acctcccagc 120
tctgttttcc atccccctca ggtccttcct cgggaggcgg cgaaggcggg ccacctgcg 180
cgtgatcctt yatgcccggc cctgccccct ccttcggggt ggaacttccc cctcaccgcc 240
agacttaagc tgaggatcgt tggatctctg gcgggggtgca gaactgagcc caggccacag 300
taccctattc acgctctgtg cttgtgccaa gggggcaatg gcggcttcct gtgttctact 360
gcacactggg cagaagatgc ctctgattgg tctgggtacc tggaagagtg agcctgggtca 420
ggtaaaagca gctgttaagt atgcccttag cgtaggctac cgccacattg attgtgctgc 480
tatctacggc aatgagcctg agattgggga ggccctgaag gaggacgtgg gaccaggcaa 540
ggcgggtgct cgggaggagc tgtttgtgac atccaagctg tggaacacca agcaccacc 600
cgaggatgtg gagcctgccc tccggaagac tctggctgac ctccagctgg agtatctgga 660
cctgtacctg atgcaactgg cttatgcctt tgagcgggga gacaaccctt tccccagaa 720
tgctgatggg actatatgct acgactccac cactacaag gagacttgga aggctctgga 780
ggcactgggt gctaaggggc tgggtgcaggc gctgggcctg tccaacttca acagtcggca 840
gattgatgac atactcagtg tggcctccgt gcgtccagct gtcttgacag tggaatgcc 900
cccatacttg gctcaaaatg agctaattgc cactgcca gcacgtggcc tggaggtaac 960
tgcttatagc cttttgggct cctctgatcg tgcattggct gatcctgatg agcctgtcct 1020
gctggaggaa ccagtagtcc tggcattggc tgaaaagtat ggccgatctc cagctcagat 1080
cttgctcagg tggcagggtc agcggaaagt gatctgcatc cccaaaagta tcactccttc 1140
tcgaatcctt cagaacatca aggtgtttga cttcaccttt agcccagaag agatgaagca 1200
gctaaatgcc ctgaacaaaa attggagata tattgtgcct atgcttacgg tggatgggaa 1260
gagagtccca agggatgcag ggcacacctc gtaccctttt aatgaccctg actgagacca 1320
cagcttcttg gcctcccttc cagctctgca gctaattagg tcctgccaca acggaaagag 1380
ggagttaata aagccattgg agcatccaaa aaaaaaaaaa aaaaaanayc tngsggccgn 1440
caagggaa 1448

```

<210> 282

<211> 827

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (725)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (800)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

182

<222> (815)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (817)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (819)
 <223> n equals a,t,g, or c

<400> 282
 ggcggacgcgt gggcggacgc gtgggtccaa gggaccccaa agctccaggg cagtttgggc 60
 gtcctgtagt tgtcccccac ggaaaggaga aggaggcaga aagaagatgg aaagaaggaa 120
 acttcaatgt ctaccttagc gatttgatcc cagtggatag agccattgaa gacaccagac 180
 ctgctggatg tgcagagcag ctagttcaca ataacctccc aaccaccagt gtcacatgt 240
 gctttgtgga tgaagtgtgg tccactctcc tgagatctgt tcacagtgtc atcaatcgct 300
 ctccctccaca cctcatcaag gagattctgc tggtagatga cttcagcacc aaagactatc 360
 taaaagataa tttggataaa tacatgtccc agtttccaaa agttcggatt cttcgccctca 420
 aagagagaca tggcttaata agggccaggc tggcaggagc acagaatgca acaggtgatg 480
 tggtgacatt tttagattct catgtggaat gtaacgttgg ttggttgga cctcttcttg 540
 aaagagttta ttttaagtaga aagaaagtgg cctgtccagt aatcgaagtc atcaatgata 600
 aggatatgag ttacatgaca gtggataact ttcaaagagg catctttgtg tggcccatga 660
 actttggttg gagaacaatt cctccagatg tcattgcaaa aaacagaatt aaagaaactg 720
 atacnataag gtgccctgtc atggctggtg ggattgggtt ctattgccaa aagttacttt 780
 ttttgaactt ggaacatacn aacccttggc cttnnangnt ttggggg 827

<210> 283
 <211> 524
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (518)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (524)
 <223> n equals a,t,g, or c

<400> 283
 ggcgatttgg ccgcctccct accgctccaa gcccagccct cagccatggc atgccccctg 60
 gatcaggcca ttggcctcct cgtggccatc ttccacaagt actccggcag ggagggtgac 120
 aagcacaccc tgagcaagaa ggagctgaag gagctgatcc agaaggagct caccatkggc 180
 tcgaagctgc aggatgctga aattgcaagg ctgatggaag acttggaccg gaacaaggac 240
 caggaggtga acttccagga gtatgtcacc ttccctggggg ccttggcttt gatctacaat 300
 gaagccctca agggctgaaa ataaataggg aagatggaga caccctctgg gggtcctctc 360

183

```

tgagtcaaat ccagtgggtgg gtaattgtac aataaatTTTt ttttgggtcaa atttataaaaa 420
aaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 480
aaaaaacaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaanac aan 524

```

<210> 284

<211> 613

<212> DNA

<213> Homo sapiens

<400> 284

```

cctcactaaa gggaacaaaa gctggagctc caccgcggtg gcggccgctc tagaactagt 60
ggatcccccg ggctgcagga attcggcacg agccgcaggc cacgagaagc tgccggtgca 120
cgtagaagac gccctcacct atctggacca ggtgaagatc cgctttggca gcgaccctgc 180
cacctacaac ggcttccttg agatcatgaa ggagttcaaa agccagagca tcgatactcc 240
tggagtcatc agacgtgtct cgcagctctt ccacgagcac cctgacctca ttgttggatt 300
caacgctttt cttccccctg gatatagaat agacattccc aagaatggca agttaaacad 360
acagtcgcct ctgacaagcc aggagaattc gcacaaccac ggggacggtg cagaggactt 420
caagcagcag gtgccgtwta aagaggacaa accccagggtg cccctggagt ccgattccgt 480
ggaattcaac aacgccatca gctatgtgaa taagattaaa acccgcttct agaccacca 540
gaaattacag gtcattcctg gagatctgca cacstwccar aargarcarc tgaacacgag 600
gggccggcca ttc 613

```

<210> 285

<211> 533

<212> DNA

<213> Homo sapiens

<400> 285

```

ggcacgagsg gcgggaacac gcggggccca agatggcggc cagccggtac cggcgTTTTt 60
ttaagctctg tgaggaatgg ccagtggacg agaccaaagc gggccgggac ttgggcgctt 120
acctgcgaca gcgggtagca caggcctttc gggagggaga gaataccag gttgcagagc 180
ctgaggcctg tgatcagatg tacgagagct tagcgcgact ccattcaaac tactacaaac 240
acaagtaccc tcgccccaga gacaccagct tcagtggcct gtcgttggaa gagtacaagc 300
tgatcctgtc cacagacacc ttggaagagc ttaaggaaat agataaaggc atgtggaaga 360
aactgcagga gaagtttgcc cccaagggtc ctgaggagga tcataaggcc tgagctcagg 420
ccttacctcg tgcacatacc taggtgtgga gtcttgtaca ttgccatcgt caataaaact 480
gccccagttt ccccttgaaa aaaaaaaaaa aaaraaaaaa gaaaaaagtc gac 533

```

<210> 286

<211> 2071

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (303)

<223> n equals a,t,g, or c

<400> 286

```

caagcggaaa ataatgatca agcggcacga ggtggagcag cagaacattc gggaggaact 60
aaataaaaag aggaccaga aggagatgga gcatgccatg ctaatccggc acgacgagtc 120

```

184

```

cmcccgagag ctagagtaca ggcagctgca cacgttacag aagctacgca tggatctgat 180
ccgttttacag caccagacgg aactggaaaa ccagctggag tacaataaga ggcgagaaaag 240
agaactgcac agaaagcatg tcatggaact tcggcaacag ccaaaaaact taaaggccat 300
ggnaatgcaa attaaaaaac agtttcagga cacttgcaaa gtacagacca aacagtataa 360
agcactcaag aatcaccagt tggaagttac tccaaagaat gagcacaaaa caatcttaaa 420
gacactgaaa gatgagcaga caagaaaact tgccattttg gcagagcagt atgaacagag 480
tataaatgaa atgatggcct ctcaagcggt acggctagat gaggctcaag aagcagaatg 540
ccaggccttg aggctacagc tccagcagga aatggagctg ctcaacgcct accagagcaa 600
aatcaagatg caaacagagg cacaacatga acgtgagctc cagaagctag agcagagagt 660
gtctctgctc agagcacacc ttgagcagaa gattgaagag gagctggctg cccttcagaa 720
ggaacgcagc gagagaataa agaacctatt ggaaaggcaa gagcgagaga ttgaaacttt 780
tgacatggag agcctcagaa tgggattttg gaattttggtt acattagatt ttcctaagga 840
ggactacaga tgagattaaa ttttttgcca ttacaaaaaa aaaaaaaaaa aaagaaaaca 900
raaaaaaatt cagaccctgc aaaaccacat tccccatttt aacgggcgtt gctctcactc 960
tctctctctc ttactcttac tgacatcgtg tcggactagt gcctgtttat tcttactcca 1020
tcaggggccc ccttcctccc ccggtgtcaa ctttcagtgc tggccaaaac ctggccgtct 1080
cttctattca cagtacacgt cacagtattg atgtgattca aaatgtttca gtgaaaactt 1140
tggagacagt tttaacaaaa ccaataaacc aacaacaaaa aaagtggatg tatattgctt 1200
taagcaatca ctcatcacc ccaatctgtg aaagtaaagc aaaaaataat aataataaat 1260
gccaaggggg agagagacac aatatccgca gccttacacc ttaactagct gctgcattat 1320
tttattttat tttatttttt tggattttat tcatcaggaa taaaaaaaac aaagttttat 1380
taaagattga aaatttgata catttttacag aaactaattg tgatgtacat atcagtgggtg 1440
acatattatt actttttttg ggacgggggg tgggtggggt gaagagatct tgtgattttt 1500
aagaacctgc tggcaagagt ttaacttgtc ttcagcatat tctgattgta tcataatcat 1560
tttctgctgt tgcagaggat gtgaatacac ttaaggagct cacagaatcc cagtagcaca 1620
aattgggctt tggcaaatcg tgtattttgt gtatagaagg aatttaagga gaggtattac 1680
ttattttcat attgtatttt aactgtttct ctgatcaaat ttttttactt cctcctcctg 1740
ttcctcccca cctccctcct tttccagttc agtattttgga gttcaacact gtctctcaat 1800
cagatcatct tgatcttttt ctttatctcc cttccccctt ctaagtocca tttcttgggtc 1860
ataaatattg cattattcac actttcaaac tgtgtatttt cttacaataa aaaatgatga 1920
aaaaaaaaaa ggctttactt cttttgcatg cacttttaaaa acaaaaacaaa acatttttca 1980
ggttccaagg aaragcatga taactgtcag agcttttaat tatatttgta aataaaagtg 2040
ttcatcacia aaaaaaaaaa aaaaaaaaaa a 2071

```

<210> 287

<211> 1966

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (56)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (788)

<223> n equals a,t,g, or c

<220>

<221> misc feature

185

<222> (1753)

<223> n equals a,t,g, or c

<400> 287

```
gaactagtct cgagtttttt ctgtctagct ccgaccggct gaggcggcgc ggcagnnggag 60
ggacggcagt ctgcrcggc tactgcagca ctgggggtgtc agttggttggc ccgaccacaga 120
acgcttcagt tctgctctgc aaggatatat aataactgat tgggtgtgccc gtttaataaaa 180
agaatatgga aactgaacag ccagaagaaa ccttcacctaa cactgaaacc aatgggtgaat 240
ttggtaaacg ccctgcagaa gatatggaag aggaacaagc atttaaaaga tctagaaaca 300
ctgatgagat ggttgaatta cgcattctgc ttcagagcaa gaatgctggg gcagtgattg 360
gaaaaggagg caagaatatt aaggctctcc gtacagacta caatgccagt gtttcagtcc 420
cagacagcag tggccccgag cgcataattga gtatcagtgc tgatattgaa acaattggag 480
aaattctgaa gaaaatcatc cctaccttgg aagagggcct gcagttgcca tcacctactg 540
caaccagcca gctcccgctc gaatctgatg ctgtggaatg cttaaattac caacactata 600
aaggaagtga ctttgactgc gagttgagggc tgttgattca tcagagtcta gcaggaggaa 660
ttattggggc caaagggtgct aaaatcaaag aacttcgaga gaacactcaa accaccatca 720
agcttttcca ggaatgctgt cctcattcca ctgacagagt tgttcttatt ggaggaaaac 780
ccgatagngt tgtagagtgc ataaagatca tccttgatct tatactctgag tctcccatca 840
aaggacgtgc acagccttat gatcccaatt ttacgatga aacctatgat tatggtgggt 900
ttacaatgat gtttgatgac cgtcgcggac gcccagtggg atttcccatg cggggaagag 960
gtgggttttga cagaatgcct cctggtcggg gtgggcgtcc catgcctcca tctagaagag 1020
attatgatga tatgagccct cgtcagaggc cacctcccc tcctcccgga cgaggcggcc 1080
ggggtggttag cagagctcgg aatcttctc ttctccacc accaccacct agaggggggag 1140
acctcatggc ctatgacaga agagggagac ctggagaccg ttacgacggc atggttgggt 1200
tcagtgtctg tgaaacttgg gactctgcaa tagatacatg gagcccatca gaatggcaga 1260
tggtcttatga accacagggc ggctccggat atgattattc ctatgcaggg ggtcgtggct 1320
catatggtga tcttggtgga cctattatta ctacacaagt aactattccc aaagatttgg 1380
ctggatctat tattggcaaa ggtggtcagc ggattaaaca aatccgtcat ggtcggggag 1440
cttcgatcaa aattgatgag cctttagaag gatccgaaga tcggatcatt accattacag 1500
gaacacagga ccagatacag aatgcacagt atttgetgca gaacagtgtg agcagtwma 1560
gwttagcttt gtgttagctt atacatacta aaacctttta aaagcttttc ttctcaattg 1620
atTTTTTtct tttagaagcc atggtgtctc aaccttttgg ggacctaaact tctaaacatt 1680
ctaatagttt gccttaattt ttcttctgct ttcttactaa aaacgargac attcaatact 1740
aatcttgcct ggnaggaagc cttgaaccaa gcaaaacttct gcatttctct ggtgaaaact 1800
gctgccaaaa ccacttgta aaaattgtac agagcctgta ggaaaatata gaaggttcca 1860
ttgggatgtt ggcctagttc tgtgtgggaa gacttagtgg attttgtttg tttttagata 1920
actaaatcgg ccaacaaatc accgttctg cctatgggac cgggcc 1966
```

<210> 288

<211> 869

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (869)

<223> n equals a,t,g, or c

<400> 288

```
gctctggcgg gcataccagc gggccctggc cgctcacccg tggaaagtac aggttyctgac 60
agctgggccc tgtggttagga ggctggtaca aggttttggg tcggttcac cctggcacca 120
```

186

```

ccaaagtgga tgcactgaag aagatgttgt tggatcaggg gggctttgcc cctgtgttttc 180
taggctgctt tctcccactg gtagggggcac ttaatggact gtcagcccag gacaactggc 240
caaactacag cgggattatc ctgatgcctt tatcaccac tactatctat ggcctgctgt 300
gcakttagcc aacttctacc tgggtccctt tcattacagg ttggccgttg tccaatgtgt 360
tgctgttatc tggaactcct acctgtcctg gaaggcacat cggctctaag cctgcctcac 420
tccatcgttt ccaccttgca gtgatgcagc ttgacctgg aacggtcaga caacctcctc 480
aaagtgggca taccagtttc cacgggggtt gggtgcccgt cagagcttaa gaggactagc 540
acctgcaat gcccctcttc actctaaaat gtacactgac tgcttttagag cccttgataa 600
tagtcttatt cccaccacat actaggcact ccataaatat ctggtgaacc ttcacgacct 660
tatcaacttt acaccatat cccagcaaat gccactcatc cccactcttc atagacacat 720
ttgttactct aacctgcctt aggtctcttg tagctccagc tcttttagaga ctcccggaac 780
ccttttatatg gtgcctcagt aaatatgtta ttaaatatgt aatccgaaa aaaaaaaaaa 840
aaaaaaaaa aaaaaaaaaa aaaaaaaan 869

```

<210> 289

<211> 1105

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<400> 289

```

cagaatgtat tcggcagaaa agggactcag gtangcccag cctgggactg agagcagaaa 60
agcattcaag atttgcaggc cttgctatgg atgcgcttaa tcaccatgga ggccagcaat 120
acctatctca gcatggcttt gatattctct acttccctggc ctttaaaaaat gacctataat 180
ttttcagttt gctttactat attttataaa gaaaattcta tcttatgggt gattgagcat 240
tgagacttat gaaggcatta ggatagatag ctcaggaatg taaaggttca gaaaagggtc 300
gttttctcag attaacaaat atgatggatt ccatggctga ccttgggtgt taaaccagga 360
ggtttcaatc tagtcctaga gttgtgtccc tctgaaaggc ccaatgccat gtaactaact 420
ttaaactgga tatatacttt gagccttact taattcacag ataagttgac ttaactcagt 480
atttttatth caattaatga aaacagtcct cttttcaacc ccagggtgtc tacatthttgc 540
tggctctccc aagtgacctt tgggtggagc caattaatga aggaatgaaa ttcactthtat 600
tgggactgtg gtattcaaca gageccacct taaccacttt ttccaatgaa gaatctccag 660
aatgataatg cccaaatatg gatggccaar aagaatttgt atctacggtg tgctthtatgt 720
gtttttgaca ctgctgtatt ctgtgtgata aagtgatttg sagctgggtc caatgtkact 780
gagtgttctc aaaratthct agtaactaag tcaacttaat tttcttaagc ctggtattac 840
tatcagcctc acatthacca cthtgattct agthththta ctgttcataa cagggcatac 900
cgagggttgg gatgagagcc tacttccctac ctcttaaggc actthcctca thatthttgce 960
atataatctt gaactgcatg ataagctgtt taaatgtcca tgactthctc cagagcaact 1020
agcaaagtat atgaccatth tgaatagagg ttagtggaag ggaaatgta gaggththta 1080
gttcagagg tacaacctc caata 1105

```

<210> 290

<211> 1982

<212> DNA

<213> Homo sapiens

<400> 290

187

```

tggatccccc gggctgcagg aattcggcac gagcagagac gtggaggcgt gagggagaac 60
atgcttggtta aatatgcagg tagattagga gacaccaaag agagattcag acacagtaag 120
gctgggatga gatcctcgaa gctgtgtttt aacaaactcc actggagagt cccatattcc 180
ctcaaatttg ggaatcacga ccctgaacca ggttgggcct gaagcagtca actgaattca 240
ctttttcgga tagtaatttg ttcccagggg cagtgacaac catgatgttc caggtttggg 300
ctggcactct gccttgaacg taggaagctc ttgatgattt gtggaatgaa tttttaaaaa 360
attactatct ggggaaaact agttggcata cagagttgta ggacagggtt tatgtgattc 420
at ttgatatt ttagtatttt ggtgtaaaag ccaacaggca aactttgccg ggtactgtgt 480
agaaactcga aaatgtgagg ccagtttgta cagttcagag gaaatgcttt aacgtagaat 540
cagatagctg gaagagatct tcgagggaaa gtaagttccc taaagtcaca tctatgtctc 600
ctagctcagt gttctttgtc attgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgat 660
tagaaagggc ttcatcctata ccttttccct tggacctgga aaaaaattt tttttatctt 720
ttcaaataaa atctattgat ttctagtaat catatktgaa tcaatgttaa agcatatata 780
gtcttatatg taaactagat tcttaagatt atktgaacct ttgagatgaa gtttacactc 840
aactaaaatc attccattga ttttattgat taacatcaat cagtatgttt aaagttattc 900
taagaagcaa tagtttattt ttaaaaacct tgtayagcaa aataacttaa aaccctttgt 960
gatatcatct taccagttta tttggtaaaa acaaacagtt atttggtatt tgtcagaatt 1020
cttcagtgcc tgctattaca gctattttcc aattactaat ttgattatac tcaactcaagg 1080
cagtgcaga tcttgaagta ctttttagca gttaagtaat attgaattgt attgaatagt 1140
ttacatagtt tattctagtc tttgaaaatt actgaacatg gacaatgtgc atgtcattga 1200
catctgcctt agaacttctg ggacaatcct gattcgagag attctatccc attattttaca 1260
tataccaaaa atactttgtt aatttaatgt gttggcttcc caactcctga acacgacaca 1320
at ttattatt tagattttgt atgggtgatt taggctatga aaacatgac atttatatgta 1380
tatagataca tttttatttg ttacaaatgt ttgagcagct cactagccca cccctcctct 1440
at ttgtgggt agagaattta ctacctttt taactatgta gttgagagca acatgtattt 1500
tgttattttt agaatggtca gtatattgct ataaaaattt aaatgagact atgaaagtta 1560
aagtattctg attctggtta aattaacgaa tatggttcca ggccctgttc tctgggtttt 1620
tgagagagaa taaaggttat gtttgtctta cctttgttat cgagtttgct gaattctttt 1680
gaacgatgat cttaaaggca caaacaccac cagccacttt gctaatttct taatagcaga 1740
tttacattgc agcaagaaaa ccatctttta tagtaacatt cagttaaaaa gaactcaatt 1800
cattgttaac ttcttaaaac agaatttgaa ctttatcaac ctcaacgtgt atataaacta 1860
gatagtcctc aatactttat caacctcaac atgtatataa actagatagt cctcaaatac 1920
tgtttgaatt taataaatgt caatttaaaa attttaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aa 1982

```

<210> 291

<211> 2329

<212> DNA

<213> Homo sapiens

<400> 291

```

tttttttact ctagggaaaa cactgacgaa tggtcagagc tcctatcctg atcttttcat 60
caaggcgcct ttcttaataa tatggttcaa ctgtgaatgt agaagtgggg gggagggggg 120
agaaaaagaa aactctggcg ttagaggata tagaaaaata taagtacaat tgttacaaat 180
aacgcgagact tcaaaaacaa aaaaatcaca acccaaacaa accaaaattt aaatgatcag 240
aattggcagc acaaaagaaa cgccctctcc tgacttgtat tgtggcagtc tgaacgcccc 300
cagaaaattg tgccaaagag tttagaaaaa taaatataca ataaaagtaa acacatacac 360
acaaaacagc aaacttcagg taactatttt ggattgcaaa caggataatt aaatgttcaa 420
acaatctgat aaaataacca tttggaaact gcttggcctt ctgttctttt atttgattga 480
ctacaatgcg gtattggtct cttgctgcac ttcaaaagca accaacaaaa caaaaacaaa 540
aaaaagtgtg tgtgtgtgaa tacacacaca cactaactag aagtcttgtg atgaaaatgg 600

```

188

```

cacttggaag aggttttatt tttccactga agttgaaggt taataaaatg gtgtcaaacg 660
tcccctgggc acacacttga atattttttt agaagtgtga tgtggtatga ttaccataaa 720
tcagacttaa ttattttccc ttttacaagg gaacagggca tcctgaattt tagagccttt 780
cagcaataag aagggatgtt ggtgagcttt gatcctcttt tggttttgca gttgttagga 840
gtttttgctg gcattttgaa tatgctgctt tcagaaaaac caaggaagtt ttaaaattgc 900
ttcctgggtc ttagaggact aaaaacaaga ccctcattcc cactttcatt tccactctag 960
caaaaactgg gcttgcggtt ttctccaact cctcggttat atcctccctt ccatgtccaa 1020
gccttccatt cctaagtggg attggctcag ttttgcccat ccatatggca gcattctctaa 1080
tagctcttgt acaggggtatc agatattgtg ccttttgggtg ccaggttcaa agtcaagtgc 1140
cgatctatga accagtgtac aaaaaaaaaa aaatccaggt atttgaagga gagacgctcc 1200
attgtgaata aagagctcat accagctcct aagccctatt aagaagaggc ctgggtcctct 1260
aatgccttgt ttccatttca gttgttcttt gagagacaga atgatgtact aaccattcgt 1320
gattattaag ataggggttg gtcagggctt agggaggggg cagaaatatt ggggatagaa 1380
aaaaaatctg atcattcctc agtgctaccc atttctgtcc tgtgtgggct gcttagctag 1440
acagcaggag aataaaagtac accgagaacc ataatgaaaa aaccttccgt gtgttttgtc 1500
atgttttgtt ccagggaagc agttgatgag tgctgttact aatgctttct cccagatcca 1560
ttcagtgggtg gagaggagga aaatgggctg gttggatgtg gtcttgggtg cttgcagtta 1620
ctctgcactg gttatgcatt taattctcct cttttctagt taaccttttg ccagtgggtt 1680
ttccatagtc tgggtatttg kccttatatc agttatacca cctaaggcaa ctgggtgcaa 1740
aatgcattct gttcactcac tgtctgggcc ttccccacc tagtcttggc acattccttc 1800
aagaatgtag ttaccgtctg cttgggaaga tgtcagtgc aatgtgaaga taatgggcat 1860
cggactaggc ttttggtttkc cacaagtggc agctgcctgt atcaattaca tttattaatt 1920
ttgcttttca tttttccag ttctctcac ccccccttg ttgaaatgtt ggacttgctg 1980
tcagaggcaa ctgtaaatatt gccttaggga cttgtggaga aggggaattg ctcagtgtag 2040
tgttttaact ttcagaacca agcaatctat ttactcttac aaatatttaa gaagtgtgtt 2100
agtccaactt taagaaaaat ccaaactcat cagcttttga tagcatcttg gtttttgaaa 2160
caacttcaat ctgtaattgg cattcagaat gcccttggca tgccagtctg tgatggcatt 2220
taagacctgt aaaacacttg agcccaactc gattaaccaa aaccgataac caccaccttt 2280
atcttctaaa taaagtcgcg tttattttta ttttcaacaa aaaaaaaaaa 2329

```

<210> 292

<211> 2424

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (666)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1757)

<223> n equals a,t,g, or c

<400> 292

```

gatcaattct cacttaagag gccataaac aaccaacat gaaaagggtga caagcctggg 60
tttctcccag gatagggtgaa aggggttaaaa tgagtaaagc agttgagcaa acaccaaccc 120
gagcttcggg cgcagaattc ttcaccttct cttccccctt ccatctcctt tccccgggga 180
aacaacgctt cccttctggg gtgtctgttg atctgtgttt tcattttacat ctctcttaga 240
ctccgctctt gttctccagg ttttcaccag atagatttgg gggttggcggg acctgctggg 300

```

189

```

gacgtgcagg tgaaggacag gaaggggcat gtgagcgtaa atagaggtga ccagaggaga 360
gcatgagggg tggggccttg ggacccaccg gggccagtgg ctggagcttg acgtctttcc 420
tccccatggg ggtgggaggg cccccagctg gaagagcaga ctcccagctg ctaccccctc 480
ccttcccatg ggagtggcct tccatttttg gcagaatgct gactagtaga ctaacataaa 540
agatataaaa ggcaataact attgtttgtg agcaactttt ttataacttc caaaacaaaa 600
acctgagcac agttttgaag ttctagccac tcgagctcat gcatgtgaaa cgtgtgcttt 660
acgaangtgg cagctgacag acgtgggctc tgcattgccg cagcctagta gaaagtcttc 720
gttcattggc aacagcagaa cctgcctctc cgtgaagtcg tcagcctaaa atttgtttct 780
ctcttgaaga ggattctttg aaaaggctct gcagagaaat cagtacaggt tatcccgaaa 840
ggtacaagga cgcacttgta aagatgatta aaacgtatct ttcctttatg tgacgcgtct 900
ctagtgcctt actgaagaag cagtgcacct cccgtcgctc ggtgaggacg ttcccggaca 960
gtgcctcact cacctgggac tgggtatccc tcccaggktc caccaagggc tcctgctttt 1020
cagacacccc atcatcctcg cgcgtcctca cctgtctct accagggagg tgcctagctt 1080
ggtgagggtta ctctgtctcc tccaaccttt ttttgccaag gtttgtacac gactcccatc 1140
taggctgaaa acctagaagt ggaccttggt tgtgtgcatg gtgtcagccc aaagccaggc 1200
tgagacagtc ctcatatcct cttgagccaa actgtttggg tctcgttgct tcatggtatg 1260
gtctggattt gtgggaatgg ctttgcgtga gaaaggggag gagagtgggt gctgccctca 1320
gccggcttga ggacagagcc tgtccctctc atgacaactc agtggtgaag cccagtgtcc 1380
tcagcttcat gtccagtggg tggcagaagt tcatggggta gtggcctctc aaaggctggg 1440
cgcattccaa gacagccagc aggttgtctc tggaaacgac cagagttaag ctctcggtct 1500
ctctgtctgag ggtgcacctt ttctcttaga tggtagttgt cacgttatct ttgaaaactc 1560
ttggactgct cctgaggagg cctcttttcc cagtaggaag ttagatgggg gttctcagaa 1620
gtggctgatt ggaaggggac aagcttcggt tcagggggtc gccgttccat cctggttcag 1680
agaaggccga gcgtggcttt ctctagcctt gtcactgtct cctgcctgt caatcaccac 1740
ctttctcca gaggagnaaa attatctccc ctgcaaagcc cggttctaca cagatttcac 1800
aaattgtgct aagaaccgtc cgtgttctca gaaagccag tgtttttgca aagaatgaaa 1860
agggacccca tatgtagcaa aaatcagggc tgggggagag cggggttcat tccctgtcct 1920
cattggctgt ccctatgaat tgtacgtttc agagaaatct ttttctctat gtgcaacacg 1980
aagcttccag aaccataaaa tatcccgtcg ataaggaaag aaaatgtcgt tgttgttgtt 2040
tttctggaaa ctgcttgaaa tcttgcgtga ctatagagct cagaaggaca cagcccgtcc 2100
tcccctgcct gcctgattcc atggctgttg tgcctgattcc aatgctttca cgttgggttc 2160
tggcgtggga actgctctcc tttgcagccc catttcccaa gctctgttca agttaaactt 2220
atgtaagctt tccgtggcat gccggggcgcg caccacagtc cccgtctcgt aagactctgt 2280
atttggatgc caatccacag gcctgaagaa actgcttgtt gtgtatcagt aatcattagt 2340
ggcaatgatg acattctgaa aagctgcaat acttatacaa taaatcttac aattcttttg 2400
aaaaaaaaa aaaaaaaagt cgac 2424

```

<210> 293

<211> 2160

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (470)

<223> n equals a,t,g, or c

<400> 293

```

gctcgtgccg tggatgcggc tctgcaggat gaagatgaga tacagggtgga tgcattcatca 60
tttgaaagca ctgcaaataa gaaatcctcc tctcttctct caggaacccc tgcattctcag 120
ctttatccac agtctcgggg gctgggttcca aagtaaagcc agcttctcct ctcccagggc 180

```

190

```

ggaaacagca tttgccttct gagagaagag actagcaaaa agctgcagag aggattcggc 240
ccaaactcag aactgttccc ctgaggagaa gcggtggcct ctttgcagat caaccaactt 300
aatctggttg aacgtgctgt tcctaactct gcactcagcc cctctgggaa acatctttta 360
attagcatct cagaaatgca tgggtaaggt aaagtgcgat agttcaagt gaaagcaaga 420
gaatgaccag tgaccttgct tccttcccc ttgccttctt cttccccctn cctgtgctc 480
cctttctctc ctctctcctt ttctagcctg ttcttwacat ggggctccct tcttggtgaa 540
caatagggca gaatcaggrg tcaccttagc aggaccacat ctttggagcc tcgggataaa 600
atgacagtga ggttgaaaag tgaaaaccct aggaacttga ataggtgcct gttctttag 660
ggagaaatga gaaatcgcat ttggatccag gccccagggtg ggcaccatca gcagtcttgc 720
ttccatgcac ctcatgaaga agtggatctg cctttgggac ctgctcagtg aggaaatctc 780
ttccaatttc tgcttctgaa tgattcaatg ttgggagcaa tagaaataac attccctttg 840
ccttctctga gtgttttaggg aaatagcttc tttaaaacct caaaaccatg accatcctgt 900
caaagaccta agtctgtaag ctggtgccat gtccatacac catgtcactt tactcttcat 960
ttgtcaccat cttttcccat gcacgcatac tctgaacatc cttgtgtggg cccatcctct 1020
gcattccagag catgctctgc agtgggcctg ttttgtggaa gaaaggaggc tgtctctgcc 1080
ttctctgatg ggactggagt tgagggaagg agctgtattg tggcacttct gaattccccg 1140
ttttgttcca tattggtata gagagcagaa gagtagctag gcagatgcag agatggagac 1200
atgagactca gtgcagtggg cagggaagac ataacagatg gaagcaaagg aatcctgcct 1260
gccttcagca gagaattcac cgaatcctag aactgtggct cctccaggc agagcctaag 1320
atgctggtga agaatagctg tgtgattgaa taggtcaaa ggagagttca gaattcccat 1380
ttacatatta ctagtttggg ttgtaagttt tagttccttg tattattgag attcagagct 1440
tcattttatg ttggtcatta ggtgaatatt actcattttc cctcaagaga agctcataag 1500
tgtgtgtggg tgtgagagca cgatggtgcc tgtgttctgt gaatgtgtcc atatgtgtct 1560
gtaagagaga cagagaccaa gaacttgccc aattttagaa atacactaat gtgcagttgt 1620
tgctttttgt ctgtattgaa ggccattga atgactaatc caggctggaa gcattcccat 1680
gtgggtgtct gagtccatga gccaaagcctg aggggacagt gagtctccag gtctgccaca 1740
ctggtgcacc ttgctggcac ggtgcctcag gaaggtggcg actcargtgg gccttgagtt 1800
atattttaac tcagctgctc agttcccagg gcacatttct ggatcagaac ccatgggaaa 1860
caggaggtag taagtgaat gtcttagcat tctgcaaaat ggagatctgt tgtccagcgg 1920
cttatctcct ttttagtaac ccttctttct gaaccagggt cctttttcag ccttccctca 1980
tattttcttg agatcaaact ttacttcttt cttattttact aagaatttgc ctgtttgaat 2040
aagaacaaaa cgctaagggt ggtagcctaa gctgattttc tgctgggttac acgtgtctct 2100
cacaccacat ttcctcaaag ctaatctgaa ttctgtaggc taaaaatatt catgtagcaa 2160

```

<210> 294

<211> 1257

<212> DNA

<213> Homo sapiens

<400> 294

```

tcgaatgtca tcaggaatga gcagctgccc ctgcagtact tggccgatgt ggacacctct 60
gatgaggaaa gcatccgggc tcacgtgatg gcctcccacc attccaagcg gagaggccgg 120
gcgtcttctg agagtcagggt tctaggtgct grakygcgca cgraggccga tgtagaggag 180
gaggccctga ggaggaagct ggaggagctg accagcaacg tcagtgaacca ggagacytcg 240
tccgaggagg aggagtccaa ggacgaaaag gcagagccca acaggggaaa atcagttggg 300
cctctcccc aggcggaccc ggaggtggca cggctgcccc tcaaaccaac agacaggaaa 360
aaagccccc ggaccctggg gaccccgctc agtacaacag gaccacagat gaggagctgt 420
cagagctgga ggacagagtg gcagtgcagg cctcagaagt ccagcaggca gagagcgagg 480
tttcagacat tgaatccagg attkcagccc tgagggccgc aggctcacgg tgaagccctc 540
gggaaaagccc cggaggaagt caaacctccc gatatttctc cctcgagtgg ctgggaaact 600
tggcaagaga ccagaggacc caaatgcaga cccttcaagt gagggcaagg caatggctgt 660

```

191

```

gccctatctt ctgagaagaa agttcagtaa ttccctgaaa agtcaaggta aagatgatga 720
ttcttttgat cggaaatcag tgtaccgagg ctcgctgaca cagagaaacc ccaacgcgag 780
gaaaggaatg gccagccaca ccttcgcgaa acctgtggtg gccaccagt cctaacggga 840
caggacagag agacagagca gccctgcact gttttccctc caccacagcc atcctgtccc 900
tcattggctc tgtgctttcc actatacaca gtcaccgtcc caatgagaaa caagaaggag 960
caccctccac atggactccc acctgcaagt ggacagcgac attcagtcct gcactgctca 1020
cctgggttta ctgatgactc ctggctgccc caccatcctc tctgatctgt gagaaacagc 1080
taagctgctg tgacttccct ttaggacaat gttgtgtaaa tctttgaagg acacaccgaa 1140
gacctttata ctgtgatctt ttaccccttt cactcttggc tttcttatgt tgctttcatg 1200
aatggaatgg aaaaaagatg actcagttaa caccaaaaaa aaaaaaaaaa gtcgagc 1257

```

<210> 295

<211> 1117

<212> DNA

<213> Homo sapiens

<400> 295

```

gccctgagcc ccgccatggt ggtgccggag gaccagctga cccgctggca cccgcgcttc 60
aacgtggatg aagtaccoga catcgagccg gccgcgtgc cccagccacc cgccacggag 120
aagctcacca ctgctcagga ggtgctggcc cgggcccgca acctgatttc acccaggatg 180
gagaaggcct tgagtcaatt ggccctgcgy tctgctgcgc ccagcagccc cgggtctccc 240
aggccagcac tgccggctac cccaccagcc accccgcctg cagcctctcc cagtgtctctg 300
aagggggtgt cccaggatct gctggagcgg atccgagcca aggaggcaca gaagcagctg 360
gcacagatga cgcggtgccc ggagcaggag cagcggctgc agcgcttaga acggctgcct 420
gagytggccc gcgtgctgcg gagcgtcttt gtgtccgaac gcaagcctgc gctcagcatg 480
gaggtggcct gtgccaggat ggtgggcagc tgttgtacta tcatgagccc tggggaaatg 540
gagaagcacc tgctgtctct ctccgagctg ctgccggact ggctcagcct ccaccgcctc 600
cgcaccgaca cctacgtcaa gctggacaag gccgcggacc tsgcccacat cactgcacgc 660
ctggccacc agacacgtgc tgaggagggg ctgtgagcct gggggccact gtggacagac 720
gtgggcttca gaagctcgct ggccctgggc caccagcatt ttcttttatg aacatgatac 780
actttggyct tcctttcccc agcgcctctg agggccagag gcagatgtgg gctgcaggct 840
gcacagcccg agggctctct gctgcggggc gtgggcccct tcatggggct cacctggtgg 900
attcacatta aaccggtttc tgtgggcacc tctgtccttg ctgctgggtg ggaagggaag 960
ccagatccag caccctctgg ggggccatcg ggagtgtggc tggrrgtgaa gggggctctg 1020
tggcaatatg gggttgggtg gtgtgggtgg caaggccatc cctctaatc ttggaacctc 1080
tgaatatggg accttcacac gcaaagggtg actttttg 1117

```

<210> 296

<211> 468

<212> DNA

<213> Homo sapiens

<400> 296

```

tcgacccacg cgctccgccac gcgtccggag gtttttccct tggagggcaa acaaagtggc 60
agtggggacc aggggtgtccc ctgctgagaa atggagagct cttttccctt gtacttctct 120
ggggtttgcc ttgtggaacc aagtgtcttg gggaggagct cctggcagga ctccagctgt 180
tatttgtcag aggacagcta ggattgggtc accttgctc tgagttggcc ccaaagcgag 240
ctatgtcgaa ctcttctcca tctccaagca gacaaccttt gtctttacat gcaagaggga 300
tccaattatg acaggctgac ccagctgggt tcatgttttg gggttatcta ctgagtaagg 360
ctgaccttac ctgagtttct gtatgtgtat ttgcaagaca gttaatacta atccatcatc 420
cctcacagag atgtagagga tgagatgtag taacttatag cagtgtca 468

```

192

<210> 297
 <211> 464
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (80)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (458)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (461)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (464)
 <223> n equals a,t,g, or c

<400> 297
 ggacagaggt cctggaggcc ttgatgaggc ccagcaaaca ggcattctca cagctggggt 60
 tatagtcttt gggcccttn ctcagtatcc tgggaaccct gggccaggag gttacagtgg 120
 tcatcataat tgctgaagag atccccctcc ctgccccctgg gttcctgcct tccctcctca 180
 agcaggcacc caggcttttag agaagtatag ggggcttctt ccctgctggg cttaccacac 240
 tgctctcagg cctcaaacc tttcatacct ttattctttt ttttaaccaa aaaagttttt 300
 cttataaaaat aaatttttggg caaacawmaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aggggggncc nttt 464

<210> 298
 <211> 2630
 <212> DNA
 <213> Homo sapiens

<400> 298
 gctgcacttc ccaggcccca ccagccgcgg ctccggctcg tagccacag cccactgccg 60
 gcggtctggc gctgccgagg ctcggggcgc gcgcagttgg cgtctgccag tgccaagact 120
 gtgccgcccc cacagccgag gcgcgaaagg gggacgcccg gcctctgggc cgtctgcctt 180
 gctttctctt cgttgttgcg aacgccgtcc gctcaggagg cgccccgcga ccggcgcgat 240
 gagtgccaac gaggaccagg agatggaact agaagcatta cgctctattt atgaaggaga 300
 tgaaagtttt cggaatttaa gtccagtttc ttttcaatat aggatagggtg aaaatgggtga 360
 tcccaaagcc ttcttaatat agatttctctg gacagaaaca tatcccaaa cacctccaat 420
 tctatctatg aacgcttttt ttaacaacac catatcatca gctgtaaagc agagtatatt 480
 agccaagcta caggaagcag tagaagctaa tcttggaacc gctatgacct atacattggt 540

193

```

tgaatatgcc aaagacaata aagagcagtt catggagaat cacaatccca tcaattccgc 600
aacatcgata agcaatatca tctcaattga aactccta atacagcccat caagtaagaa 660
aaaagacaaa aaagaacaac tttcaaaagc ccagaagcgt aactggcaga caaaacagat 720
caciaaggag aacttcctcg aggctggaac tgggttgatg ttgtgaagca ttttaagcaa 780
actggctcta aggatgatga gtagcacttg gaatttgaga caaggaaaga gcattcttta 840
aagagtaaaa ctgggttcaa aatccttcat tactattttc tggatttgag gcgacttttt 900
ataaaacaca atttttttgta tgtttcttac attaaaaagg ttgtaagttg aaagttcatg 960
aagagatctt gttgtattaa attattttca caaacttgcc ttaataaaag gtgaaaatgt 1020
tactgttttag tatacttttat gaagccctt gagctttata aatggacagg catggggaat 1080
aagaatcagt gttaatttaa atgatcttat cctgggtgat gtgctrtttt cttaaaggag 1140
tatgaagccc ttttcaaact atcatcccag tggagcggag tactcagtga acagttactc 1200
catagtgaac tccatattaa taggcttctt ctcttaagtc ttcactctct cttttgctta 1260
attactgaac cgtaaattac ttcagagaaa tttaaatgct ggtatttgaa ctttatacat 1320
gatacttttt gtagtttctt ttaatttttg aaagatgaac tgcttccttt taataaatta 1380
atatctatct atacttttct cttgatttgg gtcaagatgt ttgatcatga gtgctttgag 1440
tggtatgtgg aataggagaa tataaaaaaca aatctgccaa atacactaga aagcatttta 1500
gtaagaaaatg ctggcccttt cttaaaacat ttctcttgca tataccagga tgggagtaaa 1560
agatgcctta atatttagtt tttgtattgt tggagacatt gattttaata aaatcctatt 1620
tatctgctgt tgtgtgcttt tagttgttgg ataactgagg tctcctaaat ggttcaacat 1680
aaaaccacat ttcaagtctt gtttcttttt ggagtgtctt ttcaagtatt caaatgtatt 1740
tctcaacctg agcatctttt taatcatata catgggagtc ttttaaatgc tgaactgtta 1800
cacatgcttg atttaaaaat aataataata gaggaacta ttggtctagt tgtgccaaaga 1860
aaagtttctg atgtttatgt gtgatgtaca gtgattttgt atatgcgccc agctttaaga 1920
acacataaaa ctattacgtc tggtaggaag attgttagtg cctcaagtta cacctgtgca 1980
gcttgggtct gagttttgat agaacagtaa acatttaaag aagttaagag cagtttgagc 2040
tgtatccgcg gtttttactc gttaactgac ttcagctaaa tagtttgaat tatagagtaa 2100
gtataattac agcaaaggag ttaatctcat tttcaaagct gtttctcatt ttatttcttg 2160
aattaatgta gagcaaaaca tgtaaaaatt caggacmact ggaatatggc aacttatgtt 2220
tcaggggtgt gtgtgggtag tatttgtggg tgtattgggt tgttttttgt ttttggagaa 2280
acatctgcta gtggaataaa atactttgtt ttgctctgaa gagactgaaa ttgttcaggc 2340
ttattatggc tcatagatta cagagaatga tgctagttag atgccaatga actattttta 2400
ctcttttttat atgaaatgta aaaatttgta ggggttcttg tgatgggtgg accctcttatt 2460
accttatgta aaacacttga acagcctcat caatattgcc gtcactgttt taacactccc 2520
agtatatctt ctcaatgtct gtttacttaa aattttgttg agtgacataa ttaataagca 2580
ataaagtctg aattatacac agaaaaaaaa aaaaaaaaaa aaaactcgag 2630

```

<210> 299

<211> 1422

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (16)

<223> n equals a,t,g, or c

194

<220>
 <221> misc feature
 <222> (1205)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1367)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1381)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1398)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1401)
 <223> n equals a,t,g, or c

<400> 299
 cggacgcgtg ggnaanaaaaa aaagaaaaag aaaaagaaaa gaaaagaaaa ggtacatcag 60
 acatgactgc ctgcatgaag tcaaacaggg taacaccagt gaagctcaag tcaagagctg 120
 tggatatttt gtctaacc aaagaagtct caagaaatca ggcagtgcag ctgctgctct 180
 cagctatcgt atccagccaa aagatgcatg atgatggagt ggtgggggaa ggccagttca 240
 gtatcctatt taaaagtaaa ctccctgaat aatggatata tgtggagata cagacataga 300
 tatatagata cagctgtaat tatttagcct caagtgcatt tctccattgc ttcacgctat 360
 gccactatgt tgcttcttta atttttttta ccttgcttag tattctatag tttgcccaac 420
 cagttttacg tccaaggaaa attagccaat gcataaaaata taaaactat gaaaggcaag 480
 gwtcaggaaa ccagagactt tgccaccaa tctcagatta ttagaaacta ggtgtcaggg 540
 tttatcaaga aggccaggaa ggccttttgg gttaagcctt acattcatga agaacctcga 600
 gggtagatgt ttgagagcat tccaaatgaa tgggtctctgg tcaaatgaat gaatgggtcaa 660
 atgaataaat ctgccctcac agagatacaa aaggaaaaagg aatataattc ataccatttg 720
 gtttaagcct tacattcatg aagaacctca agggtagatt tttgagatca ttccaaatga 780
 agtcgaatct gccctcacag agacacaaga aagggaatata attcatacac tattgcattt 840
 ttaataaaatc ttttgaaatt tgcagaatta gattgtattg tgtattttcg gttaaagtat 900
 aattgaatgt aaatatattg atgcagcacc atattttata acccagcttt agcattttctt 960
 catattttta ggaaaccccc cacctccttc ttttaagggc gcttcttgct ctctgaaatg 1020
 ccctgctaaa tgcttctctt aattatttga ataaggtagt ttggaataaa gaaagaaaaag 1080
 atcactctac atacagatag taaacttaat ttgtgatcct atatatgaga cagtataaaa 1140
 atmcaagataa gtttttagaaa gactcaaaac aatatgtaaa tgactgatgt ttgcattatt 1200
 aaggnaract tgggatgttg ggtcaagagg ggaaagtgtt agtcaatcca ctttggagca 1260
 atatcatgaa ggtcaattat aattccatat acctttcttt gatgccacag tcagagatag 1320
 atacagttgg gtggccatgg gtgtgcccac acagacaatt tttggtnaat tgtttcagac 1380
 nttcaggtct gagactgnca ntgctggggg gcctcctggg tt 1422

195

<210> 300
<211> 553
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (484)
<223> n equals a,t,g, or c

<400> 300
gccccgcggt ccgatgggttt cttctattca ggcttcaatg gacaggcacc ttcgggatca 60
aagtacagag cagtcacccat ctgatcttcc tcaaaggara acagaagttg tgagttcttc 120
tgcaaagtct gggagtcttc agactgggtt gcctgaatct tttcctttaa ctgggtggtac 180
tgaaaatttg aatacagaaa caactgatgg ctgtgtagca gatgcactgg gaggcgcctt 240
tgccacaagg tcaaaagcac aaaggggaaa ttccgtggag gagcttgaag agatggatag 300
tcaagatgct gagatgacta acacaactga gccaatggat cactcttgat ttaattagag 360
gctaataaag gcagaatggt tattgtgaat atgtaatat tgttggctgg gccacgtaac 420
ttgattagtc attaaaaatc ttgtacgtat ataaaaagat tatactctgt tattcagtgc 480
atgntagcaa gtgtgtgatt ggccatagct tttaatatac tgctgcccag gctggctctg 540
aatttctata aat 553

<210> 301
<211> 464
<212> DNA
<213> Homo sapiens

<400> 301
ctcaaaaatc accagaaaac tcatactagt gaaaaatcct ataaatgtaa tgaatgtaga 60
aaggccttta gttactgctc tgggtcttatt caatgtcagg tcattcatac tatagaaaaa 120
ccttatgaat acggtaaatg tggcaaagcc tttaggcaga ggacagacct taaaaaacat 180
cagaaaatgc ataccgarga gaaaccctat gaatgtaatg aatgtgggaa agcctttagc 240
cagagcacat atcttacaaa acacaaaaaa attcatagtg aagagaaatc aaatatacat 300
actgagtgtg gggaaaccwt twgrcaaaaac tcttcttttt tacaacaata aaaacctcac 360
actggagaga ttctctgaat gccttaagaa tttggttaat atggagaccc ttcccagggg 420
aaccagaagg aggatcgtga aaacctgttg actacttaga tgat 464

<210> 302
<211> 2018
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1997)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2012)
<223> n equals a,t,g, or c

196

<400> 302

```

gccacatccc ggcagccctc ctacckgcgc acgtggtgcc gccgctgctg cctcccgcctc 60
gccctgaacc cagtgcctgc agccatggct cccggccagc tcgccttatt tagtgtctct 120
gacaaaaccg gccttgtgga atttgcaaga aacctgaccg ctcttggttt gaactctggctc 180
gcttcgggag ggactgcaaa agctctcagg gatgctggctc tggcagtcag agatgtctct 240
gagttgacgg gatttcctga aatgttgggg ggacgtgtga aaactttgca tcctgcagtc 300
catgctggaa tcctagctcg taatattcca gaagataatg ctgacatggc cagacttgat 360
ttcaatctta taagagttgt tgcttgcaat ctctatccct ttgtaaagac agtggcttct 420
ccaggtgtaa stgttgagga ggctgtggag caaattgaca ttggtggagt aaccttactg 480
agagctgcag ccaaaaacca cgctcgagtg acagtgggtg gtgaaccaga ggactatgtg 540
gtggtgtcca cggagatgca gagctccgag agtaaggaca cctccttgga gactagacgc 600
cagttagcct tgaaggcatt cactcatacg gcacaatatg atgaagcaat ttcagattat 660
ttcaggaaac agtacagcaa aggcgtatct cagatgccct tgagatatgg aatgaaccca 720
catcagaccc ctgcccagct gtacacactg cagcccaagc tccccatcac agttctaaat 780
ggagcccttg gatttataaa cttgtgcgat gctttgaacg cctggcagct ggtgaaggaa 840
ctcaaggagg ctttaggtat tccagccgct gcctctttca aacatgtcag cccagcaggt 900
gctgctgttg gaattccact cagtgaagat gaggccaaag tctgcatggt ttatgatctc 960
tataaaaccc tcacacccat ctacagcgga tatgcaagag caagaggggc tgataggatg 1020
tcttcatttg gtgattttgt tgcattgtcc gatgtttgtg atgtaccaac tgcaaaaatt 1080
atttccagag aagtatctga tgggtataatt gccccaggat atgaagaaga agccttgaca 1140
atactttcca aaaagaaaaa tggaaactat tgtgtccttc agatggacca atcttacaaa 1200
ccagatgaaa atgaagttcg aactctcttt ggtcttcatt taagccagaa gagaaataat 1260
ggtgtcgtcg acaagtcatt atttagcaat gttgttacca aaaataaaga tttgccagag 1320
tctgccctcc gagacctcat cgtagccacc attgctgtca agtacactca gtctaactct 1380
gtgtgctacg ccaagaacgg gcaggttatc ggcattggag caggacagca gtctcgtata 1440
cactgcactc gccttgccagg agataaggca aactattggt ggcttagaca ccatccacaa 1500
gtgcttttga tgaagtttaa aacaggagtg aagagagcag aaatctccaa tgccatcgat 1560
caatatgtga ctggaacat tggcgaggat gaagatttga taaagtggaa ggcactgttt 1620
gaggaagtcc ctgagttact cactgaggca gagaagaagg aatgggttga gaaactgact 1680
gaagtttcta tcagctctga tgccttcttc cttttccgag ataacgtaga cagagctaaa 1740
aggagtggtg tggcgtagat tgcggctcct ccggttctgc tgcgtacaaa gttgtgattg 1800
aggcctgcga cgaactggga atcactcctc ctcatagcaa cttcggctct tccaccactg 1860
attttaccac acactgtttt ttggcttget tatgtgtagg tgaacagtca cgcctgaaac 1920
tttgaggata acttttttaa aaaataaaac agtatctctt aatcactgga aaaaaaaaaa 1980
aaaaaaaaaa aaaaccncgg gggggggccc gnacccca 2018

```

<210> 303

<211> 658

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (621)

<223> n equals a,t,g, or c

<400> 303

```

gacatttagg aacaattgca cttttaaagg gagagaatgc atagttgctc acatatctca 60
gtgtcagtc cctaacatgg atcagtgctt tattttgagat tacaaaacta gaaaatgacg 120
gagtcaggc taggaccaat attctgttca gtcttagata attatagaat acacattaaa 180

```

197

```

atcagatatt tgaattttct taattttgta actatttgtc attgaaagga gatactaaaa 240
aaattatata tcgtcctaga aagtacatga actaataatg catttctaaa ggtgaaaaaa 300
gaataggtat ttttctgttt aatattcaat ttatagagag tagtacgtta atttttttta 360
accccgagaag ctcaggatct tatcatttta aaagaaatta tcaccagttc tgtgtgagta 420
aataaagtat tataacactt tgttttttca tccatgatac cttgtattta cttacctgag 480
ctttttttct agggaaagaa aaatgctcag gtaataacag agccttgaaa aattkggatt 540
ttcaaaacta cctattttatg tataggcctt tagatcatct gatgttgaat actctttaag 600
tgatctaaag gcctacatat naaaagggtat ttttattaaa ttctggatta aacatttc 658

```

<210> 304

<211> 671

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (524)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (593)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (657)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (659)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (671)

<223> n equals a,t,g, or c

<400> 304

```

tttacttaat cttgcctagt cacaaaataa gatgtgcacc catggtttgg agagtcccta 60
tattagctga gcagtgagat acactatttc caaacggtgc acacctacag tagcttttga 120
aatgagccaa tcaactgtttt acttaatggt tcttatcagc atgcaaatat tgcttgaaaag 180
ttatttcctt attcactgtt ttgttagtcc attttgttag gaaacattaa ttccataaaa 240
tttgttcaga ataattaaaa gtgaacattt ggtgctgata ctcaaaaacc tacaaatgta 300
gccatttaaa aagtaacatg tttttctccc ctgctcattg cctgggagaa tgggaatttta 360
tataactacc tttcttttga aaaataacgg tcgtgtcgag ttggtggtga ttttggcatt 420
ccatcttgca ctggttttcta gtataggctt agaaataatt ggcaggtaat aatctttcca 480
gtcaagttgc aagggatgct tatttctctt caaaaaaaga catnctgcgg gattgagtag 540
aaaatttagg tcagtttggg agcttatttg aatattttct actacattgg agntagcagt 600
ctttttctgg atcagatcag tgcattggtta tctacagggt gaatgcttct tgggtgngna 660

```

198

agatctagct n

671

<210> 305

<211> 1680

<212> DNA

<213> Homo sapiens

<400> 305

```

ccaaagtgct ggaattccag gcatgagcca ctgcgcccag tctacacact aattcttggt 60
agcccaacag ctgttctgtt ctatctaccc ctcatctcac gctcaaggag tcatacctag 120
aatagttaca cacaagaggg aaactggaag ccaaacactg tacagtattg tgtagaaagt 180
cacctcccta ctctttttat ttacatgag tgctgatgtg ttttggcaga tgagctttca 240
gctgaggcct gatggaaatt gagataacct gcaaagacat aacagtattt atgagttata 300
tcttagttct tgaaattgtg gaatgcatga ttgacaatat atttttaatt tttatttttt 360
caagtaatac cagtactgtt taactatagc cagaactggc taaaattttt atattttcag 420
agttgaagtt ggtgaagaca ttcattgatt aaacaccaga tcctgaaagg ggtaaactct 480
actttgaaat gaatctgcaa tcagtatttc aaagcttttc tggtaatttt agtgatctta 540
tttgattaga ctttttcaga agtactaaat aaggaatttt aacagggttt tattaatgca 600
cagataaata gaagtacagt gaggtctata gccattttat taaaatagct taaaagtttg 660
taaaaaaatg aatctttgtt attacttaat atgttagtta agaaccctgc aagcttatat 720
ttgctagact tacaaattat tttaaatgca tttatctttt ttgacactat tcagtggaaat 780
gtgtaagcta gctaattctt gttttctgat ttaaagcact tttaaatctt atcctgcccc 840
ctaaaaacaa aaggttttga tcacaagggg aaatttaaga ttgttaacct tgtttttcag 900
aagggtact gttaattgca cataaacatg aaatgtgttt tccctgtgt actaacacat 960
tctaggcaaa attcaaactt atagtggtaa agaaacagg tgttcacttg ctgaggtgca 1020
aaaattctta agacttctgt ttgaaattgc tcaatgacta ggaaaagatg tagtagttta 1080
ctaaaattgt ttttctacca tatcaaatta aacaattcat gcctttatag ggtcaggcct 1140
acaatgaata ggtatggtgg tttcacagaa ttttaaaata gagttaagg gaagtgatgt 1200
acatttcggg ggcattaggg tagggagatg aatcaaaaaa taccctagt aatgctttat 1260
attttaatac tgcaaaagct ttacaaatgg aaaccatgca attacctgcc ttagttcttt 1320
tgtcataaaa acaatcactt ggttgggtgt attgtagcta ttacttatac agcaacattt 1380
cttcaattag cagtctagac attttataaa cagaaatctt ggaccaattg ataataattt 1440
tgactgtatt aatatttttag tgctataaaa tactatgtga atctcttaaa aatctgacat 1500
tttacagtct gtattagaca tactgttttt ataatgtttt acttctgcct taagatttag 1560
gttttttaaa tgtatttttg ccctgaatta agtggttaatt tgatggaaac tctgctttta 1620
aaatcatcat ttactgggtt ctaataaatt aaaaattaaa cttgaaaaaa aaaaaaacga 1680

```

<210> 306

<211> 782

<212> DNA

<213> Homo sapiens

<400> 306

```

gaattcggca cgagtgaagc attagaatga ttccaacact gctcttctgc accatgagac 60
caacccaggg caagatccca tcccatcaca tcagcctacc tccctcctgg ctgctggcca 120
ggatgtcgcc agcattacct tccactgcct ttctccctgg gaagcagcac agctgagact 180
gggcaccagg ccacctctgt tgggaccac aggaaagagt gtggcagcaa ctgcctggct 240
gacctttcta tcttctctag gctcaggtag tgctcctcca tgcccatggc tgggcccgtg 300
ggagaagaag ctctcatacg ccttcccact ccctctgggt tataggactt cactccctag 360
ccaacaggag aggaggcctc ctgggggttt cccagggcag taggtcaaac gacctcatca 420
cagtcttcct tcctcttcaa gcgtttcatg ttgaacacag ctctctccrc tcccttgtga 480

```

199

```

tttctgaggg tcaccactgc cagcctcagg caacatagag agcctcctgt tctttctatg 540
cttgggtctga ctgagcctaa agttgagaaa atgggtggcc aaggccagtg ccagtgtctt 600
ggggccctt tggctctccc tcaactctctg aggtccagc tggtcctggg acatgcagcc 660
aggactgtga gtctgggcas gtccaaggcc tgcaccttca agaagtggaa taaatgtggc 720
ctttgcttct gttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780
aa 782

```

```

<210> 307
<211> 1791
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (487)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (515)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1769)
<223> n equals a,t,g, or c

```

```

<400> 307
ggggattggt cctgaaacat tcacgctgtc caatctccca catttcagaa ttgggtgggag 60
tgtgcatttg attgttaata accagctggg ttacaccact ccagctgaaa gaggaagggtc 120
ttctttatac tgcagtgata ttgggaagct tgtgggctgt gccatcatcc atgtcaatgg 180
agacagccca gaggaagtgg tccgtgccac acgactggct tttgaatacc aacgccagtt 240
ccgcaaggat gtgattattg atctgtttgt ctacaggcag tgggggccaca atgagctgga 300
tgagccattc tacaccaacc ccatcatgta caaaatcatc agagctcgaa agagcattcc 360
agacacatat gcagagcacc tcattgctgg cggactcatg acgcaggagg aggtgtctga 420
aataaaatcc tctactatg ccaagttgaa tgatcactta aataacatgg cccactacag 480
gccccntgc cctgaacctg caggcccayt ggcangggcc tgggycagcc agaagsgcaa 540
wtcaccacct ggagtacagg tgtgccccctc gacctcctgc ggtttgttgg catgragtyt 600
ktagagggtg caagrgagyt gcagwtgcac agtcamctgy tgragacaca tgttcagtcc 660
agaatggaga agatgatgga cggaatcaag ctagactggg ccaccgcgga actcttgcc 720
tgggttcttt acttgctcaa ggttttaatg ttcgtctaa tggccaagat gttggtcgtg 780
gaactttcag tcagaggcat gcaatgggtg tttgccagga gacggatgac acctacatcc 840
ccctgaacca tatggaccca aatcagaagg ggtttctaga ggtcagcaac agccccctgt 900
cagaagaggc cgtcctggga ttcgaatatg ggatgagcat tgagagccca aagttactgc 960
ccctgtggga ggcacagttt ggcgatttct tcaatggtgc ccagatcatc tttgacacat 1020
tcatctcttg aggagaggcc aagtggctcc tacaaagcgg cattgtcatc ctccctccac 1080
atggctacga tggggctggg ccagaccact catcctgtcg aatagagcgt ttcctgcaga 1140
tgtgtgacag tgcggaagag ggggtggacg gagacactgt gaacatgttt gtggttcacc 1200
caacaactcc tgcacagtat ttccacttgc ttaggagaca gatgggtccg aacttcagaa 1260
aaccactcat tgttgcttcc cctaagatgt tactcargct cccggcagcc gtgtcaactc 1320
ttcaagaaat ggcaccagga acaacattta acccggtcat tggtgattca tctgtggatc 1380

```

200

```
caaaaaagggt taagaccctc gtkttctgct cgggcaaaca tttctactcc ctggtgaaca 1440
aagagaatct ctggggggcca agaagcatga ctttgccatc atccgagtag aggaactctg 1500
ccccttcccg ttggattctt tacagcaaga gatgagcarr taaaacatg ttaaagatca 1560
tatttggagt caggaggaac ctcagaacat gggtcctggg tcgtttggtt ctccaagggt 1620
tgaaaagcag ctggcctgca agctccgtct ggtggccggc cccctttgcc agtaccgct 1680
gtaggaattg gcacagttca cttgcaccag catgaagata tcctcgcaa gaccttcggt 1740
tgatgatgat tttgaaggaa catatttcnt ttaggaatgg cattaggccc t 1791
```

<210> 308

<211> 723

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (705)

<223> n equals a,t,g, or c

<400> 308

```
gggcaagacc tcatgcctaa aaaataaaga gaaagcagag taaaactgga ctctgagata 60
ygactaaagt tctgtgtgat acgtgtgcct tatttagctc aagacattcc tggagcacct 120
ataaaaaactg acttgtaatc caggctatgt ctcttttttag cttcgtaatc tttggcaagg 180
ccattggatt cttcagctgt acaattagga gactcgatca ggtgattgcc tttctcagct 240
gtcagttctc taatttcagg cttggttagt ttaggaact gaaattgcaa ttaaaacctt 300
tataaactca aactaaatca tgaattacag aaaaagtcca ttcttccaaa acttgatggt 360
accacactta caagttttaa atatgaagtc gactgtttta aggattctgc atatattcta 420
gtgtgcacat tcagaaacat ttttcttgga aaaagtaccc aacatttttt ataactgcac 480
atattaatth attgccagaa taaattgcat tgcattgtaa ataaagtcag ataattcaaa 540
tccatttgct tttatgtagt ttttcttcta aatgtcaaca ttttggaatt aaaatgttta 600
tggttttata tgagggtagg aaatcttaac tgctttgggg ggtattgttt ataggctttt 660
tgttatgggg ccggtagttt tttaataggg ggattgcccc tttcnaccgt ttggggggccc 720
ggg 723
```

<210> 309

<211> 533

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (393)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (396)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (463)

201

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (527)

<223> n equals a,t,g, or c

<400> 309

```

aattcggcac gagcgacgtg gtgctgggcg ttgggaccct actttatcta gttcgggaag 60
ttgggttgtg gggtcatacc tgtctgtctg ctcccagctt tcttggggtt cttccgacgg 120
cgtggggcct cgctaaggaa ttcccggccc ctccaggcca cggcttttagc ggtgtctttt 180
gcgagttctt cgtaagtaca tcttaaagct gtcaagatgg ttctagcaga ccttggaaga 240
aaaataacat cagcattacg ctcgttgagc aatgccacca ttatcaatga agaggtatgt 300
aaaatattgt atgraatata tatgattgta ttattgtcac tagcattggg aagatggcct 360
attcdataatc cccgtattta tatgtatttt gangtngact taatacttgt gggtaaaagc 420
ccaaaggggt taacagtagg aggggtttat tggggaatta ccnccaactc aaattacttc 480
aaccttcctt aagggatttc ccaaaaaaaaa aaaaaaccgg ggggggnccc cga 533

```

<210> 310

<211> 763

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (317)

<223> n equals a,t,g, or c

<400> 310

```

gttttgaata aagaaagaaa agtttactat ctgtatgtag agtgatctta atttgtgatc 60
ctatatatga gacagtataa aaatacagat aagttttaga aagactcaaa acaatatgta 120
aatgactgat gtttgcatta ttaaggaaaa cttgggatgt tgggtcaaga ggggaaagt 180
ttagtcaatc cactttggag caatatcatg aagggtcaatt ataattccat atacctttct 240
ttgatgccac agtcrgagat asaatacart ttgggtggcc atggatgtgc cccaatacag 300
tacacatfff tkgggttnaaa tttgttttca gatcatttca tgggaatcttt gaagtatctt 360
tgactctaac tttgacttgg tgggtggacct tccttgggtt ttataacacc taagagatat 420
ccttttagaat tacatgtatt ttagcataag gaaattgaaa aagtaaaaca tactgggttt 480
tttcaacaag accatatgta aattaaatag tgaaatgtgt atgagtttca gtagaactgt 540
accatcaaca atgtttccat aaatatgcag agttctttct tttgtattgt tattttacaat 600
attgttaaat tgaatgcatt tgcaatttct aggattctaa agaattgagt acagaaagta 660
gcaattttat tattttgatga taatatgaga attactgtgc caatactgtt ttgataaata 720
aatagatfff taaaaataaa tgtattgtac ttattagtgt agt 763

```

<210> 311

<211> 3131

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

202

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3128)

<223> n equals a,t,g, or c

<400> 311

```

gggnncaaan gctggagctc caccgnggtg cgtccgctct agaactagtg gatcccccg 60
gctgcaggat tcggcacgag gccacttctt gggggccgccg gcggggccgc tggctgcact 120
cagcgccgga gccgggagct agcggccgcc gccatgtccc accagaccgg catccaagca 180
agtgaagatg ttaaagagat ctttgccaga gccagaaatg gaaagtacag acttctgaaa 240
atatctattg aaaatgagca acttgtgatt ggatcatata gtcagccttc agattcctgg 300
gataaggatt atgattcctt tgttttacct ctgttgagg acaacaacc atgctatata 360
ttattcaggt tagattctca gaatgccag ggatatgaat ggatattcat tgcattggtct 420
ccagatcatt ctcatgttcg tcaaaaaatg ttgtatgcag caacaagagc aactctgaag 480
aaggaatttg gaggtggcca cattaaagat gaagtatttg gaacagtaaa ggaagatgta 540
tcattacatg gatataaaaa atacttgctg tcacaatctt cccctgcccc actgactgca 600
gctgaggaag aactacgaca gattaaaatc aatgaggtac agactgacgt ggggtgtggac 660
actaagcatc aaacactaca aggagtagca tttcccattt ctcgagaarc ctttcaggct 720
ttggaaaaat tgaataatag acagctcaac tatgtgcagt tggaaataga tataaaaaat 780
gaaattataa ttttgcccaa cacaacaaat acagaactga aagatttgcc aaagaggatt 840
ccaaggatt cagctcgtta ccatttcttt ctgtataaac attcccatga aggagactat 900
ttagagtcca tagtttttat ttattcaatg cctggataca catgcagtat aagagagcgg 960
atgctgtatt ctactgcaa gagccgtctg ctagaaattg tagaaagaca actacaaatg 1020
gatgtaatta gaaagatcga gatagacaat ggggatgagt tgactgcaga cttcctttat 1080
gaagaagtac atccaagca gcatgcacac aagcaaagtt ttgcaaaacc aaaaggtcct 1140
gcaggaaaaa gaggaattcg aagactaatt aggggccag cggaaactga agctactact 1200
gattaaagtc atcacattaa acattgtaat actagttttt taaaagtcca gcttttagta 1260
caggagaact gaaatcattc catgttgata taaagttagg aaaaaattg tacttttttg 1320
aaaatagcac ttttcacttc tgttgtttt taaaattaat gttatagaag actcatgatt 1380
tctatttttg agttaaagct agaaaagggt tcaacataat gtttaatttt gtcacactgt 1440
tttcatagcg ttgattccac acttcaaata cttcttaaaa ttttatacag ttgggccagt 1500
tctagaaagt ctgatgtctc aaagggtaaa cttactactt tcttgtggga cagaaagacc 1560
ttaaaatatt catattactt aatgaatatg ttaaggacca ggctagagta ttttctaagc 1620
tggaacttta gtgtgccttg gaaaaggccg caagttgctt actccgagta gctgtgctag 1680

```


203

```

ctctgtcaga ctgtaggac atgtctgcaa cttttagaaa tagtgcttta tattgcagca 1740
gtcttttata tttagactttt ttttaatagc attaaaattg cagatcagct cactctgaaa 1800
ctttaagggg accagatatt ttctatactg caggatttct gatgacattg aaagacttta 1860
aacagcctta gtaaattatc tttctaattg tctgtgaggc caaacattta tgttcagatt 1920
gaaattttaa ttaatatcat tcaaaaggaa acaaaaaatg ttgagtttta aaaatcagga 1980
ttgacttttt tctccaaaac catacattta tgggcaaatt gtgttcttta tcacttccga 2040
gcaaatactc agatttaaaa ttacttttaa gtccgtgtac ttaacaggct aacgtagata 2100
aacaccttaa taatctcagt taatactgta tttcaaaaca catttaactg ttttctaattg 2160
ctttgcatta tcagttacaa cctagagaga ttttgagcct catatttctt tgatacttga 2220
aatagagggg gctagaacac ttaatgttta atctgtttaa cctgctgcaa gagccataac 2280
tttgaggcat tttctaaatg aactgtgggg atccaggatt tgtaatttct tgatctaaac 2340
tttatgctgc ataaatcact tatcggaat gcacatttca tagtgtgaag cactcatttc 2400
taaaccttat tatctaagggt aatatatgca cttttcagaa atttgtgttc gagtaagtaa 2460
agcatattag aataattgtg gggtgacaga tttttaaaat agaatttaga gtatttgggg 2520
ttttgtttgt ttacaaataa tcagactata atattttaa atgcaaaata actgacaata 2580
atgttgcact tgtttactaa agatataagt tgttccatgg gtgtacacgt agacagacac 2640
acatacacc aaattattgc attaagaatc ctggagcaga ccatagctga agctgttatt 2700
ttcagtcagg aagactacct gtcattgaagg tataaaataa tttagaagtg aatgtttttc 2760
tgtaccatct atgtgcaatt atactctaaa ttccactaca ctacattaaa gtaaattggac 2820
attccagaat atagatgtga ttatagtctt aaactaatta ttattaaacc aatgattgct 2880
gaaaatcagt gatgcatttg ttatagagta taactcatcg tttacagtat gttttagttg 2940
gcagtatcat acctagatgg tgaataacat attcccagta aatttatata gcagtgaaga 3000
attacatgcc ttctgggtgg cattttataa gtgcatttta tatcacaata aaaatttttt 3060
ctcttttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3120
aaaaaaaaaa a                                     3131

```

```

<210> 312
<211> 940
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (135)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (890)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (929)
<223> n equals a,t,g, or c

```

```

<400> 312
aagcgtgact ctggagatgg agtccaagtt ggcggcagaa aagaaacaga cggaacaact 60
gtcacttgag ctggaagtag cacgactcca gctacaagggt ctggacttaa gttctcgggtc 120
tttgcttggc atcgnacacag aagatgctat tcaaggccga aatgagagct gtgacatata 180
aaaagaacat acttcagaaa ctacagaaaag aacaccaaag catgatgttc atcagatttg 240

```

204

```

tgataaagat gctcagcagg acctcaatct agacattgag aaaataactg agactgggtgc 300
agtgaaaccc acaggagagt gctctgggga acagtcccca gataccaatt atgagcctcc 360
aggggaagat aaaaccagg gctcttcaga atgcatttct gaattgtcat tttctgggtcc 420
taatgctttg gtacctatgg atttcctggg gaatcaggaa aatatccaaa atcttcaact 480
gcgggtaaaa gagacatcaa atgagaattt gagattactt catgtgatag aggaccgtga 540
cagaaaagtt gaaagtttgc taaatgaaat gaaagaatta gactcaaaac tccatttaca 600
ggaggtacaa ctaatgacca aaattgaagc atgcatagaa ttggaaaaaa tagttgggga 660
acttaagaaa gaaaactcag atttaagtga aaaattggaa tatttttctt gtgatcacca 720
ggagttactc cagagagtag aaacttctga aggcctcaat tctgatttag aaatgcatgc 780
agataaatca tcacgtgaag atattgggag ataatgtggc caaggtgaat gacagctggg 840
aaggagagat ttcttgatgt gggaaattga gctgagtagg gtccagatcn ggagaaagct 900
agcctttgag ccttgaagcc ctcttacnng gggaggcttg 940

```

<210> 313

<211> 850

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (848)

<223> n equals a,t,g, or c

<400> 313

```

caaagttgat ttttaacggt tgtaaagggt tgaatgttta tagaagtgca tcatgaaatt 60
ttgtgtaaat ccagatgaac tgtcattata gtactataaa ttagagatag tccataaagt 120
tggtgtgaag gagattgaaa atatttcctt tgattaaaag aaaataatta actaacttgg 180
gcttgcttgt gattgaagag ggagattaga tagtcctctg tccccccraa aaagaaacta 240
gcagagaaaag acmtaaaaaa gctctttggg gtctgttcat gtgctgtaca ttttttccgt 300
tttaatgtct tgtgtagata attcaaagtt tgaactatct ctttcttggg ataagtaata 360
atattattcaa tatggtgtat ctctgagttc aatttaaaac aatccaactc agtaatatct 420
atttttaaat acaaataccta actaaccaat taattaataa aaaggcaaga cttaacttgc 480
gtagtatttg ttctcatctg tagagaactg acattggagc aaattttaag tctccccctt 540
gaaaataagc cttgttaact gagggcgtaa tacatttccc acagatttat ccagaaacat 600
tttattagag atcttatagt agtatctcag ttccactac agctttctaa aggatgagac 660
ttgcatttaa caaaatgaca tatataatat ttttctatag ttttgcaact gaattaaagg 720
aagggtgatgt attataatgt gtagtgaggt ataaagggct agttcattct ctcccaacaa 780
gaacttagaa taaaataaca cytttttttc atgagactta cctcattttt ggtaggctat 840
ggcagttntg 850

```

<210> 314

<211> 958

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (930)

<223> n equals a,t,g, or c

<220>